Guidelines on
Prostate Cancer

A. Heidenreich (chair), P.J. Bastian, J. Bellmunt,
M. Bolla, S. Joniau, M.D. Mason, V. Matveev, N. Mottet,
T.H. van der Kwast, T. Wiegel, F. Zattoni

European
Association
of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION

1.1 Introduction

The European Association of Urology (EAU) Guidelines Group for Prostate Cancer have prepared this guidelines document to assist medical professionals assess the evidence-based management of prostate cancer. The multidisciplinary panel of experts include urologists, radiation oncologists, a medical oncologist, and a pathologist specialized in prostate cancer.

1.2 Data identification and evidence sources

The recommendations provided in the current guidelines are based on a systemic literature search performed by the panel members (1). MedLine, Embase, and Web of Science databases were searched to identify original articles, review articles and editorials addressing “epidemiology”, “risk factors”, “diagnosis”,“staging” and “treatment” of prostate cancer. The controlled vocabulary of the Medical Subject Headings(MeSH) database was used alongside a “free-text” protocol, combining “prostate cancer” with the terms“diagnosis”, “screening”, “staging”, “active surveillance”, “radical prostatectomy”, “external beam radiation”,“brachytherapy”, “androgen deprivation”, “chemotherapy”, “relapse”, “salvage treatment”, and “follow-up” to ensure sensitivity of the searches.

All articles published between January 2010 (previous update) and November 2011 were considered for review. The expert panel reviewed these records to select the articles with the highest evidence, according to a rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence (1).

Additionally, publications from the major urological (EAU, AUA) and oncological meetings (ASCO, ESMO, ASTRO) have been considered.Where possible, abstracts will be replaced by the full scientific publications when these become available. Also no major recommendations can be based on evidence from abstract only.

It must be emphasised that clinical guidelines present the best evidence available but following the recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, also taking individual circumstances and patient preferences into account.

1.3 Level of evidence and grade of recommendation

The level of evidence (LE) and grade of recommendation (GR) provided in this guideline follow the listings in Tables 1 and 2. The aim of grading the recommendations is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

**Modified from Sackett, et al. (1).*

It should be noted that when recommendations are graded, there is not an automatic relationship between the level of evidence and the grade of recommendation. The availability of RCTs may not necessarily translate into a grade A recommendation if there are methodological limitations or disparities in the published results. Conversely, an absence of high-level evidence does not necessarily preclude a grade A recommendation if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical or other reasons. In this case, unequivocal recommendations are considered helpful for the reader. Whenever this occurs, it has been clearly indicated in the text with an asterisk as ‘upgraded based on panel consensus’. The quality of the underlying scientific evidence is a very important factor, but it has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned (2-4).

The EAU Guidelines Office does not perform cost assessments, nor can they address local/national preferences in a systematic fashion. However, whenever such data are available, the expert panels will include the information.

Table 2: Grade of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

**Modified from Sackett, et al. (1).*

1.4 Publication history

The Prostate Cancer Guidelines were first published in 2001, with partial updates achieved in 2003 and 2007, followed by a full text update in 2009. Also in 2011 and 2012 a considerable number of sections of the PCa guidelines were revised. This 2013 publication includes a number of updated chapters as detailed below.

Standard procedure for EAU publications includes an annual assessment of newly published literature in this field, guiding future updates.

An ultra-short reference document is being published alongside this publication. All documents are available with free access through the EAU website Uroweb (http://www.uroweb.org/guidelines/online-guidelines/).

Summary of updated and new information

Chapter 8 “Treatment: deferred treatment (watchful waiting)”

In section 8.2.1 (Watchful waiting), the findings of the PIVOT trial have been included.

Chapter 9 “Treatment Radical Prostatectomy”

The literature has been updated and additional recommendations for lymph node dissection have been included in section 9.7 (Summary of radical prostatectomy and eLND in high-risk localized disease).

Chapter 10 “Treatment: definitive radiotherapy”

The literature has been updated, as well as the findings in section 10.10 (Guidelines for definitive radiotherapy). The text has been completely restructured, in particular in sections 10.3.2 (Neoadjuvant or adjuvant hormone therapy plus radiotherapy), 10.3.2.3 (high-risk group), 10.3.4 (The benefits of lymph-node irradiation in the prostate), 10.3.4.2 (Very high-risk PCa) and 10.7.1 (Immediate [adjuvant] postoperative external irradiation after radical prostatectomy).

Chapter 12 “Hormonal therapy; rationale and available drugs”.

The literature has been updated. The chapter has been completely restructured and a section of the text was moved into a separate chapter (Chapter 15 “Metastatic prostate cancer – Hormonal therapy”), to facilitate consultation.

Chapter 13 “Metastatic Prostate Cancer – Hormonal therapy”

The literature has been updated and the text was restructured. In particular information has been added, in sections 13.1 (Prognostic factors), and 13.4 (Indications for hormonal therapy). Also section 13.4 (indications for hormonal therapy) was revised.

Chapter 15 “Quality of life of patients with localised prostate cancer”

The literature has been updated.

Chapter 18 “Treatment of biochemical failure after treatment with curative intent”

The literature has been updated and the text has been restructured.

Chapter 19 “Treatment of biochemical failure after curative intent”.

The literature has been updated. Additional information on imaging modalities has been added, most notably in the summary at the end of section 19.4.1 (Diagnostic procedures for PSA relapse following radical prostatectomy). New data has been included in sections 19.4.2 (Diagnostic studies for PSA relapse following radiation therapy, 19.5.1 (Radiotherapy for PSA-only recurrence after radical prostatectomy) and on new techniques in section 19.6.1 (Salvage radical prostatectomy).

Chapter 20 “Castration-resistant prostate cancer (CRPC)”

The literature has been updated resulting in minor changes to the recommendations. The text has been completely restructured and a new algorithm for PSA progression following initial hormonal therapy was added in section 20.5 (Secondary hormonal therapy). New information was included in

sections 20.8 (Novel hormonal drugs targeting the endocrine pathways), 20.9 (Non-hormonal therapy), as well as in section 20.11, resulting in expanding the recommendations for salvage treatment after Docetaxel. The summary of treatment recommendations (section 20.13) was subjected to a minor revision.

New topics included in this 2012 print

- Quality of life of patients with localised prostate cancer
- Chapter 16, A section has been added on salvage high-intensity focused ultrasound (HIFU)
- Chapter 17, Section 17.10.4 RANK ligand inhibitors

1.5 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

1.6 References

1. Oxford Centre for Evidence-Based Medicine Levels of Evidence (May 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009. http://www.cebm.net/index.aspx?o=1025 [Access date January 2012]
2. Atkins D, Best D, Briss PA, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations.BMJ 2004 Jun 19;328(7454):1490. http://www.ncbi.nlm.nih.gov/pubmed/15205295
3. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 Apr;336(7650):924-6. http://www.ncbi.nlm.nih.gov/pubmed/18436948
4. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. Going from evidence to recommendations. BMJ 2008 May 10;336(7652):1049--51. http://www.bmj.com/content/336/7652/1049.long

2. BACKGROUND

Cancer of the prostate (PCa) is now recognised as one of the most important medical problems facing the male population. In Europe, PCa is the most common solid neoplasm, with an incidence rate of 214 cases per 1000 men, outnumbering lung and colorectal cancer (1). Furthermore, PCa is currently the second most common cause of cancer death in men (2). In addition, since 1985, there has been a slight increase in most countries in the number of deaths from PCa, even in countries or regions where PCa is not common (3).

Prostate cancer affects elderly men more often than young men. It is therefore a bigger health concern in developed countries with their greater proportion of elderly men. Thus, about 15% of male cancers are PCa in developed countries compared to 4% of male cancers in developing countries (4). It is worth mentioning that there are large regional differences in incidence rates of PCa. For example, in Sweden, where there is a long life expectancy and mortality from smoking-related diseases is relatively modest, PCa is the most common malignancy in males, accounting for 37% of all new cases of cancer in 2004 (5).

2.1 References

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe 2004. Ann Oncol 2005 Mar;16(3):481-8. http://www.ncbi.nlm.nih.gov/pubmed/15718248
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008 Mar-Apr;58(2):71-96. http://www.ncbi.nlm.nih.gov/pubmed/18287387
3. Quinn M, Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons. BJU Int 2002 Jul;90(2):162-73. http://www.ncbi.nlm.nih.gov/pubmed/12081758
4. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000: the global picture. Eur J Cancer 2001Oct;37(Suppl 8):S4-66. http://www.ncbi.nlm.nih.gov/pubmed/11602373
5. Persson G, Danielsson M, Rosén M, et al. Health in Sweden: The National Public Health Report 2005. Scand J Public Health 2006; 34(Suppl 67):3-10. http://sjp.sagepub.com/cgi/reprint/34/67_suppl/3.pdf

3. CLASSIFICATION

The 2009 TNM (Tumour Node Metastasis) classification for PCa is shown in Table 3 (1).

Table 3: Tumour Node Metastasis (TNM) classification of PCa*

T - Primary tumour		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1		Clinically inapparent tumour not palpable or visible by imaging
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA] level)
T2		Tumour confined within the prostate[1]
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3		Tumour extends through the prostatic capsule[2]
	T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
	T3b	Tumour invades seminal vesicle(s)
T4		Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes[3]		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
M - Distant metastasis[4]		
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

1 *Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.*

2 *Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.*

3 *Metastasis no larger than 0.2 cm can be designated pN1 mi.*

4 *When more than one site of metastasis is present, the most advanced category should be used.*

Prognostic grouping

Group I	T1a-c	N0	M0 PSA < 10	Gleason ≤ 6
	T2a	N0	M0 PSA < 10	Gleason ≤ 6
Group IIA	T1a-c	N0	M0 PSA < 20	Gleason 7
	T1a-c	N0	M0 PSA ≥ 10 < 20	Gleason ≤ 6
	T2a, b	N0	M0 PSA < 20	Gleason ≤ 7
Group IIb	T2c	N0	M0 Any PSA	Any Gleason
	T1-2	N0	M0 PSA ≥ 20	Any Gleason
	T1-2	N0	M0 Any PSA	Gleason ≥ 8
Group III	T3a, b	N0	M0 Any PSA	Any Gleason
Group IV	T4	N0	M0 Any PSA	Any Gleason
	Any T	N1	M0 Any PSA	Any Gleason
	Any T	Any N	M1 Any PSA	Any Gleason

Note: When either PSA or Gleason is not available, grouping should be determined by cT category and whichever of either PSA of Gleason is available. When neither is available, and prognostic grouping is not possible, use stage grouping.

3.1 Gleason score

The ISUP 2005 Gleason score is the current standard for grading adenocarcinoma of the prostate on core biopsy and operative specimens (2). The Gleason score is the sum of the two most common patterns (grades 1-5) of tumour growth found. The Gleason score ranges between 2 and 10, with 2 being the least aggressive and 10 the most aggressive. In needle biopsies, the worst grade should always be incorporated in the Gleason score, even if comprising < 5% of the cancer (2).

3.2 References

1. Sobin LH, Gospodariwicz M, Wittekind C (eds). TNM classification of malignant tumors. UICC International Union Against Cancer. 7th edn. Wiley-Blackwell, 2009 Dec; pp. 243-248. http://www.uicc.org/tnm/
2 Epstein JI, Allsbrook WC Jr, Amin MB, et al. ISUP grading committee. The 2005 International Society of Urologic Pathology (ISUP) Consensus Conference on Gleason grading of Prostatic Carcinoma. Am J Surg Pathol 2005 Sep;29(9):1228-42. http://www.ncbi.nlm.nih.gov/pubmed/16096414

4. RISK FACTORS

The factors that determine the risk of developing clinical PCa are not well known, although a few have been identified. There are three well-established risk factors for PCa:

- increasing age;
- ethnic origin;
- heredity.

If one first-line relative has PCa, the risk is at least doubled. If two or more first-line relatives are affected, the risk increases by 5-11-fold (1,2). A small subpopulation of individuals with PCa (about 9%) has true hereditary PCa. This is defined as three or more affected relatives, or at least two relatives who have developed early-onset disease, i.e. before age 55 (2). Patients with hereditary PCa usually have an onset 6-7 years prior to spontaneous cases, but do not differ in other ways (2).

The frequency of autopsy-detected cancers is roughly the same in different parts of the world (3). This finding is in sharp contrast to the incidence of clinical PCa, which differs widely between different geographical areas, being high in the USA and Northern Europe and low in Southeast Asia (4). However, if Japanese men move from Japan to Hawaii, their risk of PCa increases. If they move to California their risk increases even more, approaching that of American men (4) (LE: 2).

These findings indicate that exogenous factors affect the risk of progression from so-called latent PCa

to clinical PCa. Factors such as food consumption, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation (5,6) and occupational exposure have all been discussed as being aetiologically important (6). Prostate cancer may be an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, due to some specific features: high prevalence, long latency, endocrine dependency, availability of serum markers (PSA), and histological precursor lesions (atypical small acinar proliferation [ASAP] or prostatic intraepithelial neoplasia [PIN]) (5). Dietary/nutritional factors that may influence disease development include total energy intake (as reflected by body mass index), dietary fat, cooked meat, micronutrients and vitamins (carotenoids, retinoids, vitamins C, D, and E), fruit and vegetable intake, minerals (calcium, selenium), and phyto-oestrogens (isoflavonoids, flavonoids, lignans), or statins and/or cholesterol intake. Since most studies reported to date are case-control analyses, there remain more questions than evidence-based data available to answer them. Several ongoing large randomised trials are trying to clarify the role of such risk factors and the potential for successful prostate cancer prevention (7).
Several studies posed that metabolic syndrome may be involved in the pathogenesis and progression of prostate diseases such as benign prostatic hyperplasia (BPH) and PCa (8,9). Even though the underlying causes are still unclear, investigators established an association between an increase of insulin resistance and hyperinsulinemia, responsible for insulin-like growth factor 1 (IGF-1) production in the liver. IGF-1 is a potent mitogenic factor and apoptosis inhibitor that has been linked to PCa risk (10).

In summary, hereditary factors are important in determining the risk of developing clinical PCa, while exogenous factors may have an important impact on this risk. The key question is whether there is enough evidence to recommend lifestyle changes (lowered intake of animal fat and increased intake of fruit, cereals, and vegetables) in order to decrease the risk (11). There is some evidence to support such a recommendation and this information can be given to male relatives of PCa patients who ask about the impact of diet (LE: 2-3).

4.1 References

1. Jansson KF, Akre O, Garmo H, et al. Concordance of tumor differentiation among brothers with prostate cancer. Eur Urol 2012 Oct;62(4):656-61. http://www.ncbi.nlm.nih.gov/pubmed/22386193
2. Hemminki K. Familial risk and familial survival in prostate cancer. World J Urol 2012 Apr;30(2):143-8. http://www.ncbi.nlm.nih.gov/pubmed/22116601
3. Breslow N, Chan CW, Dhom G, et al. Latent carcinoma of prostate at autopsy in seven areas. The International Agency for Research on Cancer, Lyons, France. Int J Cancer 1977 Nov 15;20(5):680-8. http://www.ncbi.nlm.nih.gov/pubmed/924691
4. Kheirandish P, Chinegwundoh F. Ethnic differences in prostate cancer. Br J Cancer 2011 Aug;105(4):481-5. http://www.ncbi.nlm.nih.gov/pubmed/21829203
5. Nelson WG, De Marzo AM, Isaacs WB Prostate cancer. N Engl J Med 2003 Jul;349(4):366-81. http://www.ncbi.nlm.nih.gov/pubmed/12878745
6. Leitzmann MF, Rohrmann S. Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates. Clin Epidemiol 2012;4:1-11. http://www.ncbi.nlm.nih.gov/pubmed/22291478
7. Schmid HP, Engeler DS, Pummer K, et al. Prevention of prostate cancer: more questions than data. Recent Results Cancer Res 2007;174:101-7. http://www.ncbi.nlm.nih.gov/pubmed/17302190
8. De Nunzio C, Aronson W, Freedland SJ, et al. The correlation between metabolic syndrome and prostatic diseases. Eur Urol 2012 Mar;61(3):560-70. http://www.ncbi.nlm.nih.gov/pubmed/22119157
9. Alcaraz A, Hammerer P, Tubaro A, et al. Is there evidence of a relationship between benign prostatic hyperplasia and prostate cancer? Findings of a literature review. Eur Urol 2009 Apr;55(4):864-73. http://www.ncbi.nlm.nih.gov/pubmed/19027219
10. Price AJ, Allen NE, Appleby PN, Crowe FL, et al. Insulin-like growth factor-I concentration and risk of prostate cancer: results from the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev 2012 Sep;21(9):1531-41. http://www.ncbi.nlm.nih.gov/pubmed/22761305
11. Richman EL, Kenfield SA, Stampfer MJ, et al. Egg, red meat, and poultry intake and risk of lethal prostate cancer in the prostate-specific antigen-era: incidence and survival. Cancer Prev Res (Phila) 2011 Dec;4(12):2110-21. www.ncbi.nlm.nih.gov/pubmed/21930800

5. SCREENING AND EARLY DETECTION

Population or mass screening is defined as the examination of asymptomatic men (at risk). It usually takes place as part of a trial or study and is initiated by the screener. In contrast, early detection or opportunistic screening comprises individual case findings, which are initiated by the person being screened (patient) and/or his physician. The primary endpoint of both types of screening has two aspects:

1. Reduction in mortality from PCa. The goal is not to detect more carcinomas, nor is survival the endpoint because survival is strongly influenced by lead-time from diagnosis.
2. The quality of life is important as expressed by quality-of-life adjusted gain in life years (QUALYs).

Prostate cancer mortality trends range widely from country to country in the industrialised world (1). Decreased mortality rates due to PCa have occurred in the USA, Austria, UK, and France, while in Sweden the 5-year survival rate has increased from 1960 to 1988, probably due to increased diagnostic activity and greater detection of non-lethal tumours (2). However, this trend has not been confirmed in a similar study from the Netherlands (3). The reduced mortality seen recently in the USA is often attributed to the widely adopted aggressive screening policy, but there is still no absolute proof that prostate-specific antigen (PSA) screening reduces mortality due to PCa (4) (LE: 2).

A non-randomised screening project in Tyrol (Austria) may support the hypothesis that screening can be effective in reducing mortality from PCa. An early detection programme and free treatment have been used to explain the 33% decrease in the PCa mortality rate seen in Tyrol compared to the rest of Austria (5) (LE: 2b). In addition, a Canadian study has claimed lower mortality rates in men randomised to active PCa screening (6), though these results have been challenged (7). Positive findings attributed to screening have also been contradicted by a comparative study between the US city of Seattle area (highly screened population) and the US state of Connecticut (seldom screened population) (8). The study found no difference in the reduction in the rate of PCa mortality (LE: 2b), even allowing for the very great diversity in PSA testing and treatment.

In 2009, the long awaited results of two prospective, randomised trials were published. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial randomly assigned 76,693 men at 10 US centres to receive either annual screening with PSA and DRE, or standard care as the control. After 7 years' follow-up, the incidence of PCa per 10,000 person-years was 116 (2,820 cancers) in the screening group and 95 (2,322 cancers) in the control group (rate ratio, 1.22) (9). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screened group and 1.7 (44 deaths) in the control group (rate ratio, 1.13). The data at 10 years were 67% complete and consistent with these overall findings. The PLCO project team concluded that PCa-related mortality was very low and not significantly different between the two study groups (LE: 1b).

The European Randomized Study of Screening for Prostate Cancer (ERSPC) included a total of 162,243 men from seven countries aged between 55 and 69 years. The men were randomly assigned to a group offered PSA screening at an average of once every 4 years or to an unscreened control group. During a median follow-up of 9 years, the cumulative incidence of PCa was 8.2% in the screened group and 4.8% in the control group (10). The rate ratio for death from PCa was 0.80 in the screened group compared with the control group. The absolute risk difference was 0.71 deaths per 1,000 men. This means that 1,410 men would need to be screened and 48 additional cases of PCa would need to be treated to prevent one death from PCa. The ERSPC investigators concluded that PSA-based screening reduced the rate of death from PCa by 20%, but was associated with a high risk of over-diagnosis (LE: 1b).

Both trials have received considerable attention and comments. In the PLCO trial, the rate of compliance in the screening arm was 85% for PSA testing and 86% for DRE. However, the rate of contamination in the control arm was as high as 40% in the first year and increased to 52% in the sixth year for PSA testing and ranged from 41% to 46% for DRE. Furthermore, biopsy compliance was only 40-52% versus 86% in the ERSPC. Thus, the PLCO trial will probably never be able to answer whether or not screening can influence PCa mortality.

In an update of the Gothenburg section of the ERSPC trial, which includes 20,000 men, the authors reported a reduction in PCa mortality of 50% after a median follow-up of 14 years. However, this finding was accompanied by a substantial risk of over-diagnosis (11).

In the complete ERSCP trial, the real benefit will only be evident after 10-15 years of follow-up, especially once the 41% reduction of metastasis in the screening arm has had an impact. A longer follow-up may reduce the number needed to screen and to treat (12).

Based on the results of these two large, randomised trials, most if not all of the major urological societies conclude that at present widespread mass screening for PCa is not appropriate. Rather, early detection (opportunistic screening) should be offered to the well-informed man (*see also* Chapter 6, Diagnosis). Two key questions remain open:

- At what age should early detection start?
- What is the screening interval for PSA and DRE?

A baseline PSA determination at age 40 years has been suggested, upon which the subsequent screening interval may then be based (13) (GR: B). A screening interval of 8 years might be enough in men with initial PSA levels ≤ 1 ng/mL (14). Further, PSA testing in men older than 75 years is not recommended because its early detection would not have any clinical impact (15).

5.1 References

1. Oliver SE, May MT, Gunnell D. International trends in prostate-cancer mortality in the 'PSA-ERA'. Int J Cancer 2001 Jun;92(6):893-8. http://www.ncbi.nlm.nih.gov/pubmed/11351313
2. Helgesen F, Holmberg L, Johansson JE, et al. Trends in prostate cancer survival in Sweden, 1960 through 1988, evidence of increasing diagnosis of non-lethal tumours. J Natl Cancer Inst 1996 Sep;88(17):1216-21. http://www.ncbi.nlm.nih.gov/pubmed/8780631
3. Post PN, Kil PJ, Coebergh JW. Trends in survival of prostate cancer in southeastern Netherlands 1971-1989. Int J Cancer 1999 May;81(4):551-4. http://www.ncbi.nlm.nih.gov/pubmed/10225443
4. Ilic D, O'Connor D, Green S, et al. Screening for prostate cancer: a Cochrane systematic review. Cancer Causes Control 2007 Apr;18(3):279-85. http://www.ncbi.nlm.nih.gov/pubmed/17206534
5. Bartsch G, Horninger W, Klocker H, et al. Tyrol Prostate Cancer Screening Group. Prostate cancer mortality after introduction of prostate specific antigen mass screening in the Federal State of Tyrol, Austria. Urology 2001 Sep;58(3):417-24. http://www.ncbi.nlm.nih.gov/pubmed/11549491
6. Labrie F, Candas B, Dupont A, et al. Screening decreases prostate cancer death: first analysis of the1988 Quebec prospective randomized controlled trial. Prostate 1999 Feb;38(2):83-91. http://www.ncbi.nlm.nih.gov/pubmed/9973093
7. Boer R, Schroeder FH. Quebec randomized controlled trial on prostate cancer screening shows no evidence of mortality reduction. Prostate 1999 Jul;40(2):130-4. http://www.ncbi.nlm.nih.gov/pubmed/10386474
8. Lu-Yao G, Albertsen PC, Stanford JL, et al. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. BMJ 2002 Oct;325(7367):740. http://www.ncbi.nlm.nih.gov/pubmed/12364300
9. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009 Mar 26;360(13):1310-9. http://www.ncbi.nlm.nih.gov/pubmed/19297565
10. Schröder FH, Hugosson J, Roobol MJ, et al.Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009 Mar 26;360(13):1320-8. http://www.ncbi.nlm.nih.gov/pubmed/19297566
11. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010 Aug;11(8):725-32. http://www.ncbi.nlm.nih.gov/pubmed/20598634
12. Gulati R, Mariotto AB, Chen S, et al. Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates. J Clin Epidemiol 2011 Dec;64(12):1412-7. http://www.ncbi.nlm.nih.gov/pubmed/22032753
13. Börgermann C, Loertzer H, Hammerer P, et al. [Problems, objective, and substance of early detectionof prostate cancer]. Urologe A 2010 Feb;49(2):181-9. [Article in German] http://www.ncbi.nlm.nih.gov/pubmed/20180057
14. Roobol MJ, Roobol DW, Schröder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). Urology 2005 Feb;65(2):343-6. http://www.ncbi.nlm.nih.gov/pubmed/15708050
15. Schaeffer EM, Carter HB, Kettermann A, et al. Prostate specific antigen testing among the elderly; when to stop? J Urol 2009 Apr:181(4):1606-14;discussion 1613-4. http://www.ncbi.nlm.nih.gov/pubmed/19246059

6. DIAGNOSIS*

The main diagnostic tools to obtain evidence of PCa include DRE, serum concentration of PSA, and transrectal ultrasonography (TRUS). Its definite diagnosis depends on the histopathologic verification of adenocarcinoma in prostate biopsy cores or operative specimens.

6.1 Digital rectal examination (DRE)

Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is about 0.2 mL or larger. In about 18% of all patients, PCa is detected by a suspect DRE alone, irrespective of the PSA level (1) (LE: 2a). A suspect DRE in patients with a PSA level of up to 2 ng/mL has a positive predictive value of 5-30% (2) (LE: 2a). A suspect DRE is a strong indication for prostate biopsy as it is predictive for more aggressive (Gleason score ≥ 7) prostate cancer (3,4).

6.2 Prostate-specific antigen (PSA)

The measurement of PSA level has revolutionised the diagnosis of PCa (5). PSA is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate. For practical purposes, it is organ-specific but not cancer-specific. Thus, serum levels may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. The level of PSA as an independent variable is a better predictor of cancer than suspicious findings on DRE or TRUS (6).

There are many different commercial test kits for measuring PSA, but no commonly agreed international standard exists (7). The level of PSA is a continuous parameter: the higher the value, the more likely is the existence of PCa. The finding that many men may harbour PCa, despite low levels of serum PSA, has been underscored by recent results from a US prevention study (8) (LE: 2a). Table 4 gives the rate of PCa in relation to serum PSA for 2,950 men in the placebo-arm and with PSA values ≤ 4 ng/mL.

Table 4: Risk of PCa in relation to low PSA values

PSA level (ng/mL)	Risk of PCa	Risk of Gleason ≥ 7 PCa
0-0.5	6.6%	0.8%
0.6-1	10.1%	1.0%
1.1-2	17.0%	2.0%
2.1-3	23.9%	4.6%
3.1-4	26.9%	6.7%

The findings in Table 4 clearly demonstrate the occurrence of aggressive PCa even at very low PSA levels, precluding an optimal PSA threshold value for detecting non-palpable, but clinically significant, PCa (LE: 3). Use of nomograms may help reducing the number of unnecessary prostate biopsies (9).

Several modifications of serum PSA value have been described, which may improve the specificity of PSA in the early detection of PCa. They include: PSA density, PSA density of the transition zone, age-specific reference ranges, and PSA molecular forms. However, these derivatives and PSA isoforms (cPSA [complex PSA], proPSA [precursor isoforms of PSA], BPSA [benign PSA], iPSA [intact PSA]) have limited usefulness in the routine clinical setting and have therefore not been considered for inclusion in these guidelines.

6.2.1 Free/total PSA ratio (f/t PSA)

The free/total PSA ratio (f/t PSA) is the concept most extensively investigated and most widely used in clinical practice to discriminate BPH from PCa. The ratio is used to stratify the risk of PCa for men who have total PSA levels between 4 and 10 ng/mL and a negative DRE. In a prospective multicentre trial, PCa was found on biopsy in 56% of men with f/t PSA < 0.10, but in only 8% of men with f/t PSA > 0.25 (10) (LE: 2a). Nevertheless, the concept must be used with caution as several pre-analytical and clinical factors may influence the f/t PSA, e.g. instability of free PSA, variable assay characteristics and very large prostate size (11). For example, free PSA is unstable at both 4°C and at room temperature. In addition, assay characteristics may vary, and concomitant BPH in large prostates may result in a dilution effect (11). Furthermore, f/t PSA is of no clinical use in total serum PSA values > 10 ng/mL or during follow-up of patients with known PCa.

** Acknowledgment: Section 6.4 is partly based on the Guidelines of the AUO Study Group Urologic Oncology of the Austrian Society of Urologists and Andrologists (W. Höltl, W. Loidl, M. Rauchenwald, M. Müller, M. Klimpfinger, A. Schratter-Sehn,C. Brössner).*

*6.2.2 **PSA velocity (PSAV), PSA doubling time (PSADT)***

There are two methods of measuring PSA over time:

- PSAV, which is defined as an absolute annual increase in serum PSA (ng/mL/year) (12) (LE: 1b);
- PSADT, which measures the exponential increase of serum PSA over time, reflecting a relative change (13).

These two concepts may have a prognostic role in patients with treated PCa (14), but they have limited use in the diagnosis of PCa because of background noise (total volume of prostate, BPH), the variations in interval between PSA determinations, and acceleration/deceleration of PSAV and PSADT over time. Prospective studies have shown that these measurements do not provide additional information compared to PSA alone (15-18).

*6.2.3 **PCA3 marker***

An increasingly studied new biomarker is PCA3, detectable in urine sediments obtained after three strokes of prostatic massage during digital rectal examination. The costly Progensa urine test for PCA3 is now commercially available. The amount of the prostate-specific non-coding mRNA marker, PCA3 normalised against PSA mRNA (urine sediment) gives a PCA3 score. The PCA3 score is superior to PSA total, and percent free PSA in detection of PCa in men with elevated PSA as it shows slight but significant increases in the AUC for positive biopsies (19-22). The PCA3 score may be used together with PSA and other clinical risk factors in a nomogram or other risk stratification tools to make a decision with regard to first or repeat biopsy (23). The PCA3 score increases with prostate cancer volume, but there is conflicting data about whether the PCA3 score independently predicts the Gleason score and its use as a monitoring tool in active surveillance has not been confirmed (23). The main current indication of the PCA3 urine test may be to determine whether a man needs a repeat biopsy after an initially negative biopsy outcome, but its cost-effectiveness remains to be shown.

6.3 Transrectal ultrasonography (TRUS)

The classic picture of a hypoechoic area in the peripheral zone of the prostate will not always be seen. Gray-scale TRUS does not detect areas of PCa with adequate reliability (24). It is therefore not useful to replace systematic with targeted biopsies of suspect areas. However, additional biopsies of suspect areas may be useful.

6.4 Prostate biopsy

*6.4.1 **Baseline biopsy***

The need for prostate biopsies should be determined on the basis of the PSA level and/or a suspicious DRE. The patient's biological age, potential co-morbidities (ASA Index and Charlson Comorbidity Index), and the therapeutic consequences should also be considered (25). Risk stratification is becoming an important tool to reduce unnecessary prostate biopsies (25).

The first elevated PSA level should not prompt an immediate biopsy. The PSA level should be verified after a few weeks by the same assay under standardised conditions (i.e. no ejaculation and no manipulations, such as catheterisation, cystoscopy or TUR, and no urinary tract infections) in the same diagnostic laboratory, using the same methods (26,27) (LE: 2a).

It is now considered the standard of care to perform prostate biopsies guided by ultrasound. Although a transrectal approach is used for most prostate biopsies, some urologists prefer to use a perineal approach. The cancer detection rates of perineal prostate biopsies are comparable to those obtained for transrectal biopsies (28,29) (LE: 1b).

The ultrasound-guided perineal approach is a useful alternative in special situations, e.g. after rectal amputation.

*6.4.2 **Repeat biopsy***

The indications for a repeat biopsy are:

- rising and/or persistently elevated PSA;
- suspicious DRE (30);
- atypical small acinar proliferation (ASAP);
- extensive (multiple biopsy sites) prostatic intraepithelial neoplasia (PIN) (31).

High-grade PIN as an isolated finding is no longer considered an indication for repeat biopsy (32) (LE: 2a). A repeat biopsy should therefore be prompted by other clinical features, such as DRE findings and PSA level. If PIN is extensive (i.e. in multiple biopsy sites), this could be a reason for early repeat biopsy, because the risk of subsequent PCa is slightly increased. If clinical suspicion for PCa persists in spite of negative prostate biopsies, magnetic resonance imaging (MRI) may be used to investigate the possibility of an anterior located

PCa, followed by TRUS or MRI-guided biopsies of the suspicious area (33).

6.4.3 ***Saturation biopsy***

The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is between 30% and 43% and depends on the number of cores sampled during earlier biopsies (34) (LE: 2a). In special situations, saturation biopsy may be performed with the transperineal technique. This will detect an additional 38% of PCa. The high rate of urinary retention (10%) is a drawback (35) (LE: 2b).

6.4.4 ***Sampling sites and number of cores***

On baseline biopsies, the sample sites should be as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from suspect areas by DRE/TRUS. These should be chosen on an individual basis.

Sextant biopsy is no longer considered adequate. At a glandular volume of 30-40 mL, at least eight cores should be sampled. The British Prostate Testing for Cancer and Treatment Study has recommended 10 core biopsies (36) (LE: 2a). More than 12 cores are not significantly more conclusive (37) (LE: 1a).

6.4.5 ***Diagnostic transurethral resection of the prostate (TURP)***

The use of diagnostic TURP instead of repeat biopsies is a poor tool for cancer detection (38) (LE: 2a).

6.4.6 ***Seminal vesicle biopsy***

Indications for seminal vesicle (staging) biopsies are poorly defined. At PSA levels > 15-20 ng/mL, the odds of tumour involvement are 20-25% (39) (LE: 2a), but a biopsy is only useful if the outcome will have a decisive impact on treatment, i.e. if the biopsy result rules out radical removal for tumour involvement or radiotherapy with intent to cure.

6.4.7 ***Transition zone biopsy***

Transition zone (TZ) sampling during baseline biopsies provides a very low detection rate and TZ sampling should therefore be confined to repeat biopsies (40) (LE: 1b).

6.4.8 ***Antibiotics prior to biopsy***

Oral or intravenous antibiotics are state-of-the-art treatment. Optimal dosing and treatment time vary. Quinolones are the drugs of choice, with ciprofloxacin superior to ofloxacin (41) (LE: 1b), but in the last few years increased resistance to quinolones has been reported (42) associated with a rise in severe infectious complications after biopsy (43).

6.4.9 ***Local anaesthesia prior to biopsy***

Ultrasound-guided peri-prostatic block is state-of-the-art (44) (LE: 1b). It does not make any difference whether the depot is apical or basal. Intrarectal instillation of a local anaesthetic is clearly inferior to peri-prostatic infiltration (45) (LE: 1b).

6.4.10 ***Fine-needle aspiration biopsy***

Fine-needle aspiration biopsy is no longer state-of-the-art.

6.4.11 ***Complications***

Complications include macrohaematuria and haematospermia (Table 5) (46). Severe post-procedural infections were initially reported in < 1% of cases, but this rate has increased in the last few years as a consequence of the evolution of antibiotic resistance strains with more post-biopsy hospitalisations for infectious complications while the rate of non-infectious complications has remained stable (43).

Low-dose aspirin is no longer an absolute contraindication (47) (LE: 1b).

Table 5: Percentage given per biopsy session, irrespective of the number of cores*

Complications	% of biopsies
Haematospermia	37.4
Haematuria > 1 day	14.5
Rectal bleeding < 2 days	2.2
Prostatitis	1.0
Fever > 38.5°C (101.3°F)	0.8

Epididymitis	0.7
Rectal bleeding > 2 days ± requiring surgical intervention	0.7
Urinary retention	0.2
Other complications requiring hospitalisation	0.3

** Adapted from NCCN Guidelines Prostate Cancer Early Detection. V.s.2012 (46).*

6.5 Pathology of prostate needle biopsies

*6.5.1 **Grossing and processing***

Prostate core biopsies taken from different sites are usually sent to the pathology laboratory in separate vials and should be processed in separate cassettes. Before processing, number of cores per vial and length of each core should be recorded. There is a significant correlation between the length of prostate biopsy tissue on the histological slide and the detection rate of PCa (48). To achieve optimal flattening and alignment of individual cores, one should embed a maximum of three cores per cassette and use sponges or paper to keep the cores stretched and flat (49,50). To optimise the detection of small lesions, blocks should be cut at three levels (40). It is helpful routinely to mount intervening tissue sections in case additional immunostaining is needed.

*6.5.2 **Microscopy and reporting***

Diagnosis of prostate cancer is based on histological examination. Ancillary staining techniques (e.g. basal cell staining) and additional (deeper) sections should be considered if a suspect lesion is identified (51-53). Diagnostic uncertainty in biopsies may often be resolved by intradepartmental consultation or a second opinion from an external institution (51). Table 6 lists recommended concise terminology to report prostate biopsies (50).

Table 6: Recommended diagnostic terms to report prostate biopsy findings*

Benign/negative for malignancy. If appropriate, include a description (e.g. atrophy)
Active inflammation, negative for malignancy
Atypical adenomatous hyperplasia/adenosis, no evidence of malignancy
Granulomatous inflammation, negative for malignancy
High-grade PIN, negative for adenocarcinoma
High-grade PIN with atypical glands suspicious for adenocarcinoma
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation suspicious for cancer
Adenocarcinoma

**From Van der Kwast, 2003 (49).*
PIN = prostatic intra-epithelial neoplasia.

For each biopsy site, the proportion of biopsies positive for carcinoma and the ISUP 2005 Gleason score should be reported (54). A recent study has demonstrated the improved concordance of pattern and change of prognostic groups for the modified Gleason grading (55). According to current international convention, the (modified) Gleason score of cancers detected in prostate biopsy consists of the Gleason grade of the dominant (most extensive) carcinoma component plus the highest grade, irrespective of its extent (no 5% rule). When the carcinoma largely consists of grade 4/5 carcinoma, identification of a small portion (< 5% of the carcinoma) of Gleason grade 2 or 3 glands should be ignored. A diagnosis of Gleason score 4, or lower, should not be given on prostate biopsies (54). The presence of intraductal carcinoma and extraprostatic extension should be reported. In addition to a report of the carcinoma features for each biopsy site, an overall Gleason score based on findings in the individual biopsies is commonly provided.

The proportion (%) or length (mm) of tumour involvement per biopsy core correlates with tumour volume, extraprostatic extension, and prognosis after prostatectomy (56-58), and an extent of > 5 mm or > 50% of adenocarcinoma in a single core is used as a cut-off triggering immediate treatment versus active surveillance in patients with Gleason score 6 carcinoma. For these reasons a measure of the extent of cancer involvement (mm or %) should be provided for each core. Length of carcinoma and percentage of carcinoma involvement of the biopsy have equal prognostic impact (59).

The extent of a single, small focus of adenocarcinoma, which is located in only one of the biopsies, should be clearly stated (e.g. < 1 mm or < 1%), as this might be an indication for further diagnostic work-

up before selecting therapy as this finding is associated with an increased risk of vanishing cancer (60-62). A prostate biopsy that does not contain glandular prostate tissue should be reported as inadequate for diagnostics, except for staging biopsies.

6.6 Pathohistology of radical prostatectomy (RP) specimens

*6.6.1 **Processing of the RP specimen***

The histopathological examination of RP specimens aims to provide information about the actual pathological stage, grade, and surgical margin status of the prostate cancer. The weight and dimensions of the specimen are recorded before embedding it for histological processing. It is generally recommended that RP specimens are totally embedded to enable the best assessment of location, multifocality, and heterogeneity of the cancer.

However, for cost-effectiveness, partial embedding using a standard method may also be considered, particularly for large prostates (> 60 g). The most acceptable method includes the complete embedding of the posterior (dorsal) part of the prostate in addition to a single mid-anterior left and right section. Compared to total embedding, this method of partial embedding permitted detection of 98% of prostate cancers with a Gleason score ≥ 7 and accurate staging in 96% of cases (63).

Upon receipt in the histopathology laboratory, the entire RP specimen is inked in order to appreciate the surgical margin status. The specimen is fixed by immersion in buffered formalin for a few days, preferably prior to incision of the sample, as incision causes distortion of the tissue. Fixation can be enhanced by injecting formalin using 21-gauge syringes, which provides a more homogeneous fixation and sectioning after 24 hours (64). After fixation, the apex is removed and cut with (para)sagittal or radial sections; the shave method is not recommended (65). Separate removal and sagittal sectioning of the bladder neck is optional. The remainder of the RP specimen is generally cut in transverse sections at 3-4 mm steps, perpendicularly to the posterior surface. The resultant tissue slices can be embedded and processed either as whole-mounts or after quadrant sectioning. Whole-mount processing provides better topographic visualisation of the carcinoma and faster histopathological examination. However, it is a more time-consuming and more expensive technique that requires specialised equipment and personnel. Although whole-mount sectioning may be necessary for research, its advantages do not outweigh its disadvantages for routine sectioning.

6.6.1.1 Recommendations for processing a prostatectomy specimen

Total embedding of a prostatectomy specimen is preferred, either by conventional (quadrant sectioning) or by whole-mount sectioning.
The entire surface of RP specimens should be inked before cutting to evaluate the surgical margin status.
The apex should be separately examined using the cone method with sagittal or radial sectioning.

*6.6.2 **RP specimen report***

The pathology report provides essential information on the prognostic characteristics relevant for making clinical decisions (Table 7). As a result of the complex information provided on each RP specimen, the use of synoptic-(like) or checklist reporting is recommended (Table 8). Synoptic reporting of surgical specimens results in more transparent and complete pathology reporting (66).

Table 7: Information provided by the pathology report

Typing (> 95% of PCa represents conventional (acinar) adenocarcinoma)
Grading according to the Gleason score
(Sub)staging and surgical margin status of the tumour
If appropriate, location and extent of extraprostatic extension, presence of bladder neck invasion, laterality of extraprostatic extension or seminal vesicle invasion, location and extent of positive surgical margins
Additional information may be provided on multifocality, diameter of the dominant tumour and zonal location (transition zone, peripheral zone, anterior horn) of the dominant tumour

Table 8: Example checklist - reporting of prostatectomy specimens

Histological type
Type of carcinoma, e.g. conventional acinar, ductal, etc.
Histological grade
Primary (predominant) grade
Secondary grade
Tertiary grade (if applicable)
Total/global Gleason score
Approximate percentage of Gleason grade 4 or 5 (optional)
Tumour quantitation (optional)
Percentage of prostatic gland involved
Tumour size of dominant nodule (if identified), greatest dimension in mm
Pathological staging (pTNM)
Presence of extraprostatic extension (indicate focal or extensive) • If present, specify site(s) • Presence of seminal vesicle invasion
If applicable, regional lymph nodes • Location • Number of lymph nodes retrieved • Number of lymph nodes involved
Surgical margins
Presence of carcinoma at margin • If present, specify sites and extra- or intraprostatic involvement
Other
If identified, presence of angioinvasion
Location (site, zone) of dominant tumour (optional)
Perineural invasion (optional) • If present, specify extra- or intraprostatic location

6.6.2.1 Gleason score

Grading of conventional prostatic adenocarcinoma using the (modified) Gleason score system (54) is the single strongest prognostic factor for clinical behaviour and treatment response. The Gleason score is therefore one of the parameters incorporated in nomograms that predict the risk of recurrence after prostatectomy (67).

6.6.2.2 Interpreting the Gleason score

The Gleason score is the sum of the most dominant and second most dominant (in terms of volume) Gleason grade. If only one grade is present, the primary grade is doubled. If a grade comprises ≤ 5% of the cancer volume, this grade is not incorporated in the Gleason score (5% rule). Both the primary and the secondary grade are reported in addition to the Gleason score (e.g. Gleason score 7 [4 + 3]). A global Gleason score is

given when there are multiple tumours, but a separate tumour focus with a higher Gleason score should also be mentioned. A tertiary Gleason grade 4 or 5, particularly if exceeding 5% of the prostate cancer volume, is an unfavourable prognostic indicator for biochemical recurrence. The presence of the tertiary grade and its approximate proportion of the cancer volume should also be reported (68), in addition to the Gleason score.

6.6.2.3 Definition of extraprostatic extension

The TNM staging system of the International Union Against Cancer (UICC) is recommended for pathological staging of prostate carcinoma (65,69). Pathologic substaging of pT2 prostate cancer is optional, since it does not correlate with clinical T2 substage and it lacks prognostic significance (70).

Extraprostatic extension is the recommended term for the presence of tumour beyond the confines of the prostate. Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or bulging out beyond the contours of the prostate gland, e.g. at the neurovascular bundle or the anterior prostate. Bladder neck invasion is also considered to be an extraprostatic extension.

It is useful to report not only the location, but also the extent of extraprostatic extension because extension is related to the risk of recurrence. There are no well-established and internationally accepted definitions of the terms 'focal' and 'non-focal' or 'extensive extraprostatic extension'. Some authors describe focal as 'a few glands' (71) or extension < 1 high-power field (72), whereas others measure the depth of extent in mm (73). Currently, it is considered clinically useful to report the extent of extraprostatic extension (e.g. less or more than 1 high-power field or 1 mm) (74).

At the apex of the prostate gland, tumour mixed with skeletal muscle does not constitute extraprostatic extension. In the bladder neck, microscopic invasion of small fibres of smooth muscle is not equated to (gross) bladder wall invasion, because it does not carry independent prognostic significance for PSA recurrence (75,76) and should be recorded as extraprostatic extension (pT3a). A positive margin at the bladder neck should be reported as an extraprostatic extension (pT3a) with positive margin and not as pT4 disease. Stage pT4 can only be assigned when the tumour invades the muscle wall of the bladder as determined by the urologist (77).

6.6.3 ***Prostate cancer volume***

The independent prognostic value of the volume of PCa in RP specimens has not been established (72,78-81). Nevertheless, a PCa volume cut-off of 0.5 mL continues to be an important parameter to distinguish insignificant from clinically relevant cancer (78). Continued improvement in radioimaging of the prostate gland has allowed more accurate measurement of cancer volume before surgery. Therefore, it may be recommended to assess the greatest dimension of the dominant tumour nodule, if identified, or to provide a rough estimate of the percentage of cancer tissue in the prostate.

6.6.4 ***Surgical margin status***

Surgical margin status is an independent risk factor for biochemical recurrence. Margin status is positive if tumour cells are in touch with the ink on the surface of the specimen. Margin status is negative if tumour cells are very close to the inked surface of the margin (79) or when they are at the surface of the tissue lacking any ink.

If the tissue has severe crush artifacts (usually at the apex), it may not be possible to assign a surgical margin status (82). Surgical margin status is independent of the pathological stage and a positive margin is not evidence of extraprostatic extension (83). There is insufficient evidence to prove a relationship between the extent of positive margin and the risk of recurrence (72). However, some indication must be given of the multifocality and extent of margin positivity, such as the linear extent in millimetres, or number of blocks with positive margin involvement.

6.6.5 ***Other factors***

According to the College of American Pathologists consensus statement (84), additional potential biomarkers have not been sufficiently studied to demonstrate their additional prognostic value and clinical usefulness outside the standard patient care setting (category III), including perineural invasion, neuroendocrine differentiation, microvessel density, nuclear roundness, chromatin texture, other karyometric factors, proliferation markers, prostate-specific antigen derivatives, and other factors (e.g. oncogenes, tumour suppressor genes, or apoptosis genes).

6.7 References

1. Richie JP, Catalona WJ, Ahmann FR, et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. Urology 1993 Oct:42(4):365-74. http://www.ncbi.nlm.nih.gov/pubmed/7692657

2. Carvalhal GF, Smith DS, Mager DE, et al. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng/ml or less. J Urol 1999 Mar;161:835-9. http://www.ncbi.nlm.nih.gov/pubmed/10022696
3. Okotie OT, Roehl KA, Han M, et al Characteristics of prostate cancer detected by digital rectal examination only. Urology 2007 Dec;70(6):1117-20. http://www.ncbi.nlm.nih.gov/pubmed/18158030
4. Gosselaar C, Roobol MJ, Roemeling S, et al. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. Eur Urol 2008 Sep;54(3):581-8. http://www.ncbi.nlm.nih.gov/pubmed/18423977
5. Stamey TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 1987 Oct;317(15):909-16. http://www.ncbi.nlm.nih.gov/pubmed/2442609
6. Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol 1994 May;151(5):1283-90. http://www.ncbi.nlm.nih.gov/pubmed/7512659
7. Semjonow A, Brandt B, Oberpenning F, et al. Discordance of assay methods creates pitfalls for the interpretation of prostate-specific antigen values. Prostate Suppl 1996;7:3-16. http://www.ncbi.nlm.nih.gov/pubmed/8950358
8. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med 2004 May 27;350(22):2239-46. http://www.ncbi.nlm.nih.gov/pubmed/15163773
9. Dong F, Kattan MW, Steyerberg EW, et al. Validation of pretreatment nomograms for predicting indolent prostate cancer: efficacy in contemporary urological practice. J Urol 2008 Jul;180(1):150-4; discussion 154. http://www.ncbi.nlm.nih.gov/pubmed/18485398
10. Catalona WJ, Partin AW, Slawin KM, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicentre clinical trial. JAMA 1998 May 20;279(19):1542-7. http://www.ncbi.nlm.nih.gov/pubmed/9605898
11. Stephan C, Lein M, Jung K, et al. The influence of prostate volume on the ratio of free to total prostate specific antigen in serum of patients with prostate carcinoma and benign prostate hyperplasia. Cancer 1997 Jan;79(1):104-9. http://www.ncbi.nlm.nih.gov/pubmed/8988733
12. Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA 1992 Apr 22-29;267(16):2215-20. http://www.ncbi.nlm.nih.gov/pubmed/1372942
13. Schmid H-P, McNeal JE, Stamey TA. Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. Cancer 1993 Mar 15;71(6):2031-40. http://www.ncbi.nlm.nih.gov/pubmed/7680277
14. Arlen PM, Bianco F, Dahut WL, et al. Prostate Specific Antigen Working Group. Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. J Urol 2008 Jun;179(6):2181-5; discussion 2185-6. http://www.ncbi.nlm.nih.gov/pubmed/18423743
15. Heidenreich A. Identification of high-risk prostate cancer: role of prostate-specific antigen, PSA doubling time, and PSA velocity. Eur Urol 2008 Nov;54(5):976-7; discussion 978-9. http://www.ncbi.nlm.nih.gov/pubmed/18640768
16. Ramirez ML, Nelson EC, Devere White RW, et al. Current applications for prostate-specific antigen doubling time. Eur Urol 2008 Aug;54(2):291-300. http://www.ncbi.nlm.nih.gov/pubmed/18439749
17. O'Brien MF, Cronin AM, Fearn PA, et al. Pretreatment prostate-specific antigen (PSA) velocity and doubling time are associated with outcome but neither improves prediction of outcome beyond pretreatment PSA alone in patients treated with radical prostatectomy. J Clin Oncol 2009 Aug 1;27(22):3591-7. http://www.ncbi.nlm.nih.gov/pubmed/19506163
18. Vickers AJ, Savage C, O'Brien MF, et al. Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. J Clin Oncol 2009 Jan 20;27(3):398-403. http://www.ncbi.nlm.nih.gov/pubmed/19064972

19. Deras IL, Aubin SM, Blase A, et al. PCA3: a molecular urine assay for predicting prostate biopsy outcome. J Urol 2008 Apr;179(4):1587-92.
http://www.ncbi.nlm.nih.gov/pubmed/18295257
20. Hessels D, Klein Gunnewiek JMT, van Oort I, et al. DD3 (PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. Eur Urol 2003 Jul;44(1):8-15; discussion 15-6.
http://www.ncbi.nlm.nih.gov/pubmed/12814669
21. Nakanishi H, Groskopf J, Fritsche HA, et al. PCA3 molecular urine assay correlates with prostate cancer tumor volume: implication in selecting candidates for active surveillance. J Urol 2008 May;179(5):1804-9; discussion 1809-10.
http://www.ncbi.nlm.nih.gov/pubmed/18353398
22. Hessels D, van Gils MP, van Hooij O, et al Predictive value of PCA3 in urinary sediments in determining clinico-pathological characteristics of prostate cancer. Prostate 2010 Jan 1;70(1):10-6.
http://www.ncbi.nlm.nih.gov/pubmed/19708043
23. Auprich M, Bjartell A, Chun FK, et al. Contemporary role of prostate cancer antigen 3 in the management of prostate cancer. Eur Urol 2011 Nov;60(5):1045-54.
http://www.ncbi.nlm.nih.gov/pubmed/21871709
24. Lee F, Torp-Pedersen ST, Siders DB, et al. Transrectal ultrasound in the diagnosis and staging of prostate cancer. Radiology 1989 Mar;170(3 Pt 1):609-15.
http://www.ncbi.nlm.nih.gov/pubmed/2644656
25. Roobol MJ, Steyerberg EW, Kranse R, et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. Eur Urol 2010 Jan;57(1):79-85.
http://www.ncbi.nlm.nih.gov/pubmed/19733959
26. Eastham JA, Riedel E, Scardino PT, et al. Polyp Prevention Trial Study Group. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. JAMA 2003 May 28:289(20):2695-700.
http://www.ncbi.nlm.nih.gov/pubmed/12771116
27. Stephan C, Klaas M, Muller C, et al. Interchangeability of measurements of total and free prostate-specific antigen in serum with 5 frequently used assay combinations: an update. Clin Chem 2006 Jan;52(1):59-64.
http://www.ncbi.nlm.nih.gov/pubmed/16391327
28. Hara R, Jo Y, Fujii T, et al. Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. Urology 2008 Feb;71(2):191-5.
http://www.ncbi.nlm.nih.gov/pubmed/18308081
29. Takenaka A, Hara R, Ishimura T, et al. A prospective randomized comparison of diagnostic efficiency between transperineal and transrectal 12-core prostate biopsy. Prostate Cancer Prostatic Dis 2008 June;11:134-8.
http://www.ncbi.nlm.nih.gov/pubmed/17533394
30. Epstein JI, Herawi M. Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. J Urol 2006 Mar:175(3 Pt 1):820-834.
http://www.ncbi.nlm.nih.gov/pubmed/16469560
31. Merrimen JL, Jones G, Walker D, et al. Multifocal high grade prostatic intraepithelial neoplasia is a significant risk factor for prostatic adenocarcinoma. J Urol 2009 Aug;182(2):485-90.
http://www.ncbi.nlm.nih.gov/pubmed/19524976
32. Moore CK, Karikehalli S, Nazeer T, et al. Prognostic significance of high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation in the contemporary era. J Urol 2005 Jan:173(1):70-2.
http://www.ncbi.nlm.nih.gov/pubmed/15592031
33. Lemaitre L, Puech P, Poncelet E, et al. Dynamic contrast-enhanced MRI of anterior prostate cancer: morphometric assessment and correlation with radical prostatectomy findings. Eur Radiol 2009 Feb;19(2):470-80.
http://www.ncbi.nlm.nih.gov/pubmed/18758786
34. Walz J, Graefen M, Chun FK, et al. High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series. Eur Urol 2006 Sep:50(3):498-505.
http://www.ncbi.nlm.nih.gov/pubmed/16631303
35. Moran BJ, Braccioforte MH, Conterato DJ. Re-biopsy of the prostate using a stereotactic transperineal technique. J Urol 2006 Oct:176(4 Pt 1):1376-81.
http://www.ncbi.nlm.nih.gov/pubmed/16952636
36. Donovan J, Hamdy F, Neal D, et al. ProtecT Study Group. Prostate Testing for Cancer and Treatment (ProtecT) feasibility study. Health Technol Assess 2003:7(14):1-88.
http://www.ncbi.nlm.nih.gov/pubmed/12709289

37. Eichler K, Hempel S, Wilby J, et al. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol 2006 May;175(5):1605-12. http://www.ncbi.nlm.nih.gov/pubmed/16600713
38. Zigeuner R, Schips L, Lipsky K, et al. Detection of prostate cancer by TURP or open surgery in patients with previously negative transrectal prostate biopsies. Urology 2003 Nov:62(5):883-7. http://www.ncbi.nlm.nih.gov/pubmed/14624913
39. Linzer DG, Stock RG, Stone NN, et al. Seminal vesicle biopsy: accuracy and implications for staging of prostate cancer. Urology 1996 Nov:48(5):757-61. http://www.ncbi.nlm.nih.gov/pubmed/8911521
40. Pelzer AE, Bektic J, Berger AP, et al. Are transition zone biopsies still necessary to improve prostate cancer detection? Results from the tyrol screening project. Eur Urol 2005 Dec:48(6):916-21; discussion 921. http://www.ncbi.nlm.nih.gov/pubmed/16126324
41. Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. BJU Int 2000 Apr:85(6):682-5. http://www.ncbi.nlm.nih.gov/pubmed/10759665
42. Cuevas O, Oteo J, Lázaro E, et al. Spanish EARS-Net Study Group. Significant ecological impact on the progression of fluoroquinolone resistance in Escherichia coli with increased community use of moxifloxacin, levofloxacin and amoxicillin/clavulanic acid. J Antimicrob Chemother 2011 Mar;66(3):664-9. http://www.ncbi.nlm.nih.gov/pubmed/21172788
43. Loeb S, Carter HB, Berndt SI, et al. Complications after prostate biopsy: data from SEER-medicare. J Urol 2011 Nov;186(5):1830-4. http://www.ncbi.nlm.nih.gov/pubmed/21944136
44. von Knobloch R, Weber J, Varga Z, et al. Bilateral fine-needle administered local anaesthetic nerve block for pain control during TRUS-guided multi-core prostate biopsy: a prospective randomised trial. Eur Urol 2002 May;41(5):508-14; discussion 514. http://www.ncbi.nlm.nih.gov/pubmed/12074792
45. Adamakis I, Mitropoulos D, Haritopoulos K, et al. Pain during transrectal ultrasonography guided prostate biopsy: a randomized prospective trial comparing periprostatic infiltration with lidocaine with the intrarectal instillation of lidocaine-prilocain cream. World J Urol 2004 Oct;22(4):281-4. http://www.ncbi.nlm.nih.gov/pubmed/14689224
46. NCCN Clinical Practice Guidelines in Oncology™ Prostate Cancer Early Detection, V.2.2012. Page 15. www.nccn.org
47. Giannarini G, Mogorovich A, Valent F, et al. Continuing or discontinuing low-dose aspirin before transrectal prostate biopsy: results of a prospective randomized trial. Urol 2007 Sep;70(3):501-5. http://www.ncbi.nlm.nih.gov/pubmed/17688919
48. Iczkowski KA, Casella G, Seppala RJ, et al. Needle core length in sextant biopsy influences prostate cancer detection rate. Urology 2002 May;59(5):698-703. http://www.ncbi.nlm.nih.gov/pubmed/11992843
49 Van der Kwast TH, Lopes C, Santonja C, et al. Members of the pathology committee of the European Randomised Study of Screening for Prostate Cancer. Guidelines for processing and reporting of prostatic needle biopsies. J Clin Pathol 2003 May;56(5):336-40. http://www.ncbi.nlm.nih.gov/pubmed/12719451
50. Rogatsch H, Moser P, Volgger H, et al. Diagnostic effect of an improved preembedding method of prostate needle biopsy specimens. Hum Pathol 2000 Sep;31(9):1102-7. http://www.ncbi.nlm.nih.gov/pubmed/11014578
51. Novis DA, Zarbo RJ, Valenstein PA. Diagnostic uncertainty expressed in prostate needle biopsies. A College of American Pathologists Q-probes Study of 15,753 prostate needle biopsies in 332 institutions. Arch Pathol Lab Med 1999 Aug;123(8):687-92. http://www.ncbi.nlm.nih.gov/pubmed/10420224
52. Iczkowski KA. Current prostate biopsy interpretation: criteria for cancer, atypical small acinar proliferation, high-grade prostatic intraepithelial neoplasia, and use of immunostains. Arch Pathol Lab Med 2006 Jun;130(6):835-43. http://www.ncbi.nlm.nih.gov/pubmed/16740037
53. Reyes AO, Humphrey PA. Diagnostic effect of complete histologic sampling of prostate needle biopsy specimens. Am J Clin Pathol 1998 Apr;109(4):416-22. http://www.ncbi.nlm.nih.gov/pubmed/9535395

54. Epstein JI, Allsbrook WC Jr, Amin MB, et al. ISUP grading committee. The 2005 International Society of Urologic Pathology (ISUP) Consensus Conference on Gleason grading of Prostatic Carcinoma. Am J Surg Pathol 2005 Sep;29(9):1228-42.
http://www.ncbi.nlm.nih.gov/pubmed/16096414
55. Billis A, Guimaraes MS, Freitas LL, et al. The impact of the 2005 international society of urological pathology consensus conference on standard Gleason grading of prostatic carcinoma in needle biopsies. J Urol 2008;180(2):548-52; discussion 552-3.
http://www.ncbi.nlm.nih.gov/pubmed/18550106
56. Sebo TJ, Cheville JC, Riehle DL, et al. Predicting prostate carcinoma volume and stage at radical prostatectomy by assessing needle biopsy specimens for percent surface area and cores positive for carcinoma, perineural invasion, Gleason score, DNA ploidy and proliferation, and preoperative serum prostate specific antigen: a report of 454 cases. Cancer 2001 Jun;91(11):2196-204.
http://www.ncbi.nlm.nih.gov/pubmed/11391602
57. Grossklaus DJ, Coffey CS, Shappell SB, et al. Percent of cancer in the biopsy set predicts pathological findings after prostatectomy. J Urol 2002 May;167(5):2032-5; discussion 2036.
http://www.ncbi.nlm.nih.gov/pubmed/11956432
58. Freedland SJ, Terris MK, Csathy GS, et al. Search Database Study Group. Preoperative model for predicting prostate specific antigen recurrence after radical prostatectomy using percent of biopsy tissue with cancer, biopsy Gleason grade and serum prostate specific antigen. J Urol 2004 Jun; 171(6 Pt 1):2215-20.
http://www.ncbi.nlm.nih.gov/pubmed/15126788
59. Brimo F, Vollmer RT, Corcos J, et al. Prognostic value of various morphometric measurements of tumour extent in prostate needle core tissue. Histopathology 2008 Aug;53(2):177-83.
http://www.ncbi.nlm.nih.gov/pubmed/18752501
60. Herkommer K, Kuefer R, Gschwend JE, et al. Pathological T0 prostate cancer without neoadjuvant therapy: clinical presentation and follow-up. Eur Urol 2004 Jan;45(1):36-41.
http://www.ncbi.nlm.nih.gov/pubmed/14667513
61. Postma R, de Vries SH, Roobol MJ, et al. Incidence and follow-up of patients with focal prostate carcinoma in 2 screening rounds after an interval of 4 years. Cancer 2005 Feb 15;103(4):708-16.
http://www.ncbi.nlm.nih.gov/pubmed/15648082
62. Trpkov K, Gao Y, Hay R, et al. No residual cancer on radical prostatectomy after positive 10-core biopsy: incidence, biopsy findings, and DNA specimen identity analysis. Arch Pathol Lab Med 2006 Jun;130(6):811-6.
http://www.ncbi.nlm.nih.gov/pubmed/16740032
63. Sehdev AE, Pan CC, Epstein JI. Comparative analysis of sampling methods for grossing radical prostatectomy specimens performed for nonpalpable (stage T1c) prostatic adenocarcinoma. Hum Pathol 2001 May;32(5):494-9.
http://www.ncbi.nlm.nih.gov/pubmed/11381367
64. Ruijter ET, Miller GJ, Aalders TW, et al. Rapid microwave-stimulated fixation of entire prostatectomy specimens. Biomed-II MPC Study Group. J Pathol 1997 Nov;183(3):369-75.
http://www.ncbi.nlm.nih.gov/pubmed/9422995
65. Epstein JI, Allsbrook WC Jr, Amin MB, et al. ISUP grading committee. The 2005 International Society of Urologic Pathology (ISUP) Consensus Conference on Gleason grading of Prostatic Carcinoma. Am J Surg Pathol 2005 Sep;29(9):1228-42.
http://www.ncbi.nlm.nih.gov/pubmed/16096414
66. Chan NG, Duggal A, Weir MM, et al. Pathological reporting of colorectal cancer specimens: a retrospective survey in an academic Canadian pathology department. Can J Surg 2008 Aug;51(4): 284-8.
http://www.ncbi.nlm.nih.gov/pubmed/18815652
67. Partin AW, Mangold LA, Lamm DM, et al. Contemporary update of the prostate cancer staging nomograms (Partin tables) for the new millennium. Urology 2001 Dec;58(6):843-8.
http://www.ncbi.nlm.nih.gov/pubmed/11744442
68. Harnden P, Shelley MD, Coles B, et al. Should the Gleason grading system for prostate cancer be modified to account for high-grade tertiary components? A systematic review and meta-analysis. Lancet Oncology 2007 May;8(5):411-9.
http://www.ncbi.nlm.nih.gov/pubmed/17466898
69. Ohori M, Kattan M, Scardino PT, et al. Radical prostatectomy for carcinoma of the prostate. Mod Pathol 2004 Mar;17(3):349-59.
http://www.ncbi.nlm.nih.gov/pubmed/14765206

70. Van der Kwast TH, Amin MB, Billis A, et al. ISUP Prostate Cancer Group. International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 2: T2 substaging and prostate cancer volume. Mod Pathol 2011 Jan;24(1):16-25.
http://www.ncbi.nlm.nih.gov/pubmed/20818340
71. Epstein JI, Carmichael MJ, Pizov G, et al. Influence of capsular penetration on progression following radical prostatectomy: a study of 196 cases with long-term followup. J Urol 1993 Jul;150(1):135-41.
http://www.ncbi.nlm.nih.gov/pubmed/7685422
72. Marks M, Koch MO, Lopez-Beltran A, et al. The relationship between the extent of surgical margin positivity and prostate specific antigen recurrence in radical prostatectomy specimens. Hum Pathol 2007 Aug;38(8):1207-11.
http://www.ncbi.nlm.nih.gov/pubmed/17490720
73. Sung MT, Lin H, Koch MO, et al. Radial distance of extraprostatic extension measured by ocular micrometer is an independent predictor of prostate-specific antigen recurrence: A new proposal for the substaging of pT3a prostate cancer. Am J Surg Pathol 2007 Feb;31(2):311-8.
http://www.ncbi.nlm.nih.gov/pubmed/17255778
74. Magi-Galluzzi C, Evans AJ, Delahunt B, et al. ISUP Prostate Cancer Group. International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 3: extraprostatic extension, lymphovascular invasion and locally advanced disease. Mod Pathol 2011 Jan;24(1):26-38.
http://www.ncbi.nlm.nih.gov/pubmed/20802467
75. Aydin H, Tsuzuki T, Hernandez D, et al. Positive proximal (bladder neck) margin at radical prostatectomy confers greater risk of biochemical progression. Urology 2004 Sep;64(3):551-5.
http://www.ncbi.nlm.nih.gov/pubmed/15351591
76. Ploussard G, Rotondo S, Salomon L. The prognostic significance of bladder neck invasion in prostate cancer: is microscopic involvement truly a T4 disease? BJU Int 2009;105(6):776-81.
http://www.ncbi.nlm.nih.gov/pubmed/19863529
77. Hoedemaeker RF, Vis AN, Van Der Kwast TH. Staging prostate cancer. Microsc Res Tech 2000 Dec;51(5):423-9.
http://www.ncbi.nlm.nih.gov/pubmed/11074612
78. Stamey TA, Yemoto CM, McNeal JE, et al. Prostate cancer is highly predictable: a prognostic equation based on all morphological variables in radical prostatectomy specimens. J Urol 2000 Apr;163(4):1155-60.
http://www.ncbi.nlm.nih.gov/pubmed/10737486
79. Epstein JI, Amin M, Boccon-Gibod L, et al. Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens. Scand J Urol Nephrol Suppl 2005 May;216:34-63.
http://www.ncbi.nlm.nih.gov/pubmed/16019758
80. Kikuchi E, Scardino PT, Wheeler TM, et al. Is tumor volume an independent prognostic factor in clinically localized prostate cancer? J Urol 2004 Aug;172(2):508-11.
http://www.ncbi.nlm.nih.gov/pubmed/15247716
81. Van Oort IM, Witjes JA, Kok DE, et al. Maximum tumor diameter is not an independent prognostic factor in high-risk localized prostate cancer. World J Urol 2008 Jun;26(3):237-41.
http://www.ncbi.nlm.nih.gov/pubmed/18265988
82. Evans AJ, Henry PC, Van der Kwast TH, et al. Interobserver variability between expert urologic pathologists for extraprostatic extension and surgical margin status in radical prostatectomy specimens. Am J Surg Pathol 2008 Oct;32(10):1503-12.
http://www.ncbi.nlm.nih.gov/pubmed/18708939
83. Chuang AY, Epstein JI. Positive surgical margins in areas of capsular incision in otherwise organ-confined disease at radical prostatectomy: histologic features and pitfalls. Am J Surg Pathol 2008 Aug;32(8):1201-6.
http://www.ncbi.nlm.nih.gov/pubmed/18580493
84. Bostwick DG, Grignon DJ, Hammond ME, et al. Prognostic factors in prostate cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000 Jul;124(7):995-1000.
http://www.ncbi.nlm.nih.gov/pubmed/10888774

7. CLINICAL STAGING

The primary extension assessment of prostate cancer (PCa) is usually made by DRE, PSA measurement, and bone scan, supplemented with computed tomography (CT) or MRI and chest X-ray in specific situations.

7.1 T-staging

The first level is the assessment of local tumour stage, where the distinction between intracapsular (T1-T2) and extraprostatic (T3-T4) disease has the most profound impact on treatment decisions. DRE often underestimates the tumour extension; a positive correlation between DRE and pathological tumour stage was found in fewer than 50% of cases (1). However, more extensive examinations for adequate T-staging are only recommended in selected cases when more precise staging directly affects the treatment decision, i.e. when curative treatment is an option.

Serum PSA levels increase with advancing stage. Nevertheless, when PSA level is measured in an individual patient, it appears to have a limited ability to predict the final pathological stage accurately. Due to the production of PSA by benign and malignant prostatic tissue, there is no direct relationship between serum PSA concentration and the clinical and pathological tumour stage (2). A combination of serum PSA level, Gleason score on prostate biopsy and clinical T-stage, however, has been proven to be more useful in predicting the final pathological stage than the individual parameters per se (3).

The ability of the molecular forms of PSA to predict T-stage is controversial and their routine measurement is not indicated (4,5). The most commonly used method for viewing the prostate is TRUS. However, only 60% of tumours are visible with TRUS, and the remainder are not recognised due to their isoechogenicity. In a large multi-institutional study, TRUS was no more accurate at predicting organ-confined disease than was DRE (6). These findings were supported by another large study, which showed that there was no meaningful superiority of TRUS over DRE (7). A combination of DRE and TRUS can detect T3a PCa more accurately than either method alone (8) (LE: 3).

Three-dimensional TRUS (3D-TRUS) claimed to have better staging accuracy than 2-D techniques (9). Several adjuncts to 3D greyscale TRUS have been investigated. A greater sensitivity for cancer detection has been achieved with the addition of power colour Doppler and contrast agents (10-12). Unfortunately, all TRUS techniques remain largely operator-dependent and are not able to differentiate between T2 and T3 tumours with sufficient accuracy to be recommended for routine use in staging.

Seminal vesicle invasion is predictive of local relapse and distant failure. Seminal vesicle biopsies may be used to increase the accuracy of pre-operative staging (13). This is not recommended as a first-line examination, but should be reserved for patients with a substantial risk of seminal vesicle invasion in whom a positive seminal vesicle biopsy would modify treatment decisions. Patients with a clinical stage greater than T2a and a serum PSA level of more than 10 ng/mL could be candidates for seminal vesicle biopsies (14,15). Patients with any of the basal biopsies positive for cancer are more likely to have positive seminal vesicle biopsies (16).

Of the prostate needle biopsy parameters examined, the percentage of tissue with cancer was the strongest predictor for positive surgical margins, seminal vesicle invasion and non-organ-confined disease (17). An increased number of biopsies involved with tumour independently predicts extraprostatic extension, margin involvement and lymph node invasion (18).

In a multivariate analysis, the best risk predictors of extracapsular extension on one side were the overall average of positive biopsy cores being 15% or greater, and the average from three ipsilateral biopsies being 15% or greater. When used in combination, these two factors yielded a model with a positive predictive value of 37%, and a negative predictive value of 95%. The high negative predictive value of the side-specific model identifies patients who are good candidates for nerve-sparing surgery (19). Furthermore, it may be useful to correlate the bioptic Gleason score with the final pathological stage: about 70% of patients have localised disease when the biopsy Gleason score is ≤ 6 (20).

It has been shown that transperineal three-dimensional prostate mapping biopsy (3D-PMB) provides more accurate determination of the extent and location of tumour compared to ultrasound guided 10-12 core biopsy, with Gleason score upgrading in 27.2% and up-staging in 45.6% of cases (21). The technique improves the differentiation between clinically significant cancers and low risk disease. Unlike transrectal saturation biopsy, 3D-PMB has acceptable morbidity.

Both CT and MRI are now of a high technical standard, but neither modality is sufficiently reliable to make their use mandatory in the assessment of local tumour invasion (22,23). Endorectal MRI (e-MRI) may allow for more accurate local staging by complementing the existing clinical variables by improvements in spatial characterisation of the prostatic zonal anatomy and molecular changes (24). Image quality and localisation improves significantly with e-MRI compared with external coil MRI (25). When compared with DRE and TRUS

prostate biopsy findings, e-MRI contributes significant incremental value for local PCa staging (26), particularly in the pre-operative identification of extraprostatic extension (EPE) and seminal vesicle invasion (SVI) when interpreted by dedicated genitourinary radiologists (27,28).

Endorectal MRI could impact on the decision to preserve or resect the neurovascular bundle (NVB) at the time of radical surgery (27,29,30).

When assessed for the ability to predict organ-confined PCa, the contribution of e-MRI to staging nomograms was significant in all risk categories, but the greatest benefit was seen in the intermediate and high risk groups (31). The combination of dynamic contrast-enhanced MRI and T2-weighted MR imaging yields improved assessment of EPE and better results for PCa staging compared with either technique independently (32) (LE: 3).

MR spectroscopic imaging (MRSI) allows for the assessment of tumour metabolism by displaying the relative concentrations of citrate, choline, creatinine and polyamines. Differences in the concentrations of these chemical metabolites between normal and malignant prostate tissues allow for better tumour localisation within the peripheral zone, increasing the accuracy of EPE detection among less-experienced readers, and decreasing interobserver variability (33). Furthermore, correlations have been demonstrated between the metabolic signal pattern and a pathological Gleason score, suggesting the potential for a non-invasive assessment of PCa aggressiveness (34).

Despite the proposed accuracy and benefit of e-MRI and MRSI in PCa characterisation and localisation, e-MRI has several limitations that hamper its widespread application in PCa staging, e.g. difficulties in interpreting signal changes related to post-biopsy haemorrhage and inflammatory changes of the prostate, and the unquantifiable but significant inter- and intra-observer variability seen between both non-dedicated and dedicated radiologists that may lead to under- or overestimation of tumour presence and the local extent of disease (LE: 3). The overall accuracy of ^{11}C-choline positron emission tomography (PET) in defining local tumour stage (pT2 and pT3a-4) has been reported to be around 70%. PET tends to understage PCa, and has a limited value for making treatment decisions in patients with clinically localised PCa, especially if a nerve-sparing procedure is being considered (35) (LE: 2b).

7.2 N-staging

N-staging should be performed only when the findings will directly influence a treatment decision. This is usually the case in patients for whom potentially curative treatments are planned. High PSA values, stages T2b-T3 disease, poor tumour differentiation and peri-neural tumour invasion have been associated with a higher risk of the presence of nodal metastases (3,36,37). The measurement of PSA level alone is unhelpful in predicting the presence of lymph node metastases for an individual patient.

The nomograms could be used to define a group of patients with a low risk of nodal metastasis, i.e. < 10% (38). In such cases, patients with a serum PSA level of less than 20 ng/mL, stage T2a or less, and a Gleason score of 6 or less may be spared N-staging procedures before potentially curative treatment (3).

The extent of the Gleason 4 pattern in sextant biopsies has also been used to define the risk of N1 disease. If any core had a predominant Gleason 4 pattern, or > three cores any Gleason 4 pattern, the risk of nodal metastases was found to be 20-45%. For the remaining patients, the risk was 2.5%, supporting the idea that nodal staging is unnecessary in selected patients (39).

In the current published literature, the results indicate that CT and MRI perform similarly in the detection of pelvic lymph node metastases, although CT seems to be slightly superior (40) (LE: 2a). In either case, the decision about whether nodal involvement is present rests solely on whether there is enlargement of the investigated lymph nodes A threshold of 1 cm in the short axis for the oval nodes, and 0.8 cm for the round nodes, has been recommended as the criteria for the diagnosis of lymph node metastases (41).

A fine-needle aspiration biopsy (FNAB) might provide a decisive answer in cases of positive imaging results. However, the lymph node can be difficult to reach because of the anatomical position. In addition, FNAB is not a highly sensitive staging procedure, and a false-negative rate of 40% has been reported (41).

High-resolution MRI with lymphotrophic ultra-small super-paramagnetic iron oxide particles (USPIO) was more recently suggested in the detection of small and otherwise occult lymph node metastases in patients with PCa (42,43).

In asymptomatic patients with newly diagnosed PCa and a serum PSA level of less than 20 ng/mL, the likelihood of positive findings on CT or MRI is approximately 1% (32). CT scanning may therefore be warranted in patients with a very high risk of harbouring lymph node metastases, as the specificity of a positive scan is high (93-96%). Radio-immunoscintigraphy and PET have been investigated in order to improve the diagnosis of metastatic disease to the lymph nodes. Both methods are still under investigation, and further evaluation is needed before they can be recommended for routine use in clinical practice, especially as negative results should be interpreted with caution (44).

The results obtained using ^{18}F-choline PET/CT scans for initial N-staging were discouraging, especially in terms of inability to detect small metastases/micrometastases (< 5 mm) (45). Furthermore,

^{11}C-choline PET/CT has quite a low sensitivity for the detection of lymph node metastases, but performed better than clinical nomograms, with equal sensitivity and better specificity (46).

The gold standard for N-staging is operative lymphadenectomy, either by open or laparoscopic techniques. It is worth pointing out that recent studies with more extensive lymphadenectomy have shown that the obturator fossa is not always the primary site for metastatic deposits in the lymph nodes, and pelvic lymph node dissection that is limited to the obturator fossa will therefore miss about 50% of lymph node metastases (47,48). When deciding on pelvic lymph node dissection, extended lymphadenectomy should be considered, despite its disadvantages: it requires surgical experience; it is time-consuming; and it often leads to more complications than the limited procedures. Furthermore, it may fail to identify lymph node metastases, however present, even outside the region of extended dissection (49).

The primary removal of the so-called sentinel lymph node (SLN), defined as the first lymph node that receives lymphatic drainage from PCa, has the main aim of reducing the eventual morbidity associated with an extended pelvic node dissection, while preserving maximal sensitivity for diagnosis of metastatic disease (50) (LE: 3) (*see section 9.7* Treatment: radical prostatectomy, indication and extent of eLND).

7.3 M-staging

The axial skeleton is involved in 85% of patients who die from PCa (51). The presence and extent of bone metastases accurately reflect the prognosis for an individual patient. Elevated skeletal alkaline phosphatase levels may indicate the presence of bony metastasis in 70% of affected patients (52). Furthermore, the measurement of skeletal alkaline phosphatase and PSA at the same time increases clinical effectiveness to approximately 98% (53). In a prospective study, multiple regression analysis showed the extent of bone disease to be the only variable influencing the serum levels of skeletal alkaline phosphatase and PSA. However, in contrast to serum PSA, skeletal alkaline phosphatase demonstrated a statistical correlation with the extent of bone disease (54).

Early detection of bone metastases will alert the clinician to the possible complications inherent in skeletal destruction. Bone scintigraphy remains the most sensitive method of assessing bone metastases, being superior to clinical evaluation, bone radiographs, serum alkaline phosphatase measurement and prostatic acid phosphatase (PAP) determination (55,56). Technetium diphosphonates are the optimum radiopharmaceuticals currently available because of their extremely high bone-to-soft tissue ratio (57).

Increased ^{18}F-fluoride uptake in malignant bone lesions reflects the increase in regional blood flow and bone turnover that characterise these lesions.

Studies have shown that ^{18}F-fluoride PET/CT is a highly sensitive and specific imaging modality for detection of bone metastases (58,59). However, no definitive results have been obtained and therefore no final recommendations can be made (60).

Besides bone, PCa may metastasise to any organ, but most commonly it affects distant lymph nodes, lung, liver, brain and skin. Clinical examination, chest X-ray, ultrasound, CT and MRI scans are appropriate methods of investigation, but only if symptoms suggest the possibility of soft-tissue metastasis.

The need for reliable serum markers to improve the pre-treatment staging of patients with PCa has long been recognised. At present, PSA is the marker of choice. A pre-treatment serum PSA level greater than 100 ng/mL has been found to be the single most important indicator of metastatic disease, with a positive predictive value of 100% (61). Furthermore, it has helped to reduce the number of patients with newly diagnosed PCa who require a bone scan. Patients with a low serum PSA concentration have only rarely been found to harbour detectable skeletal metastases. The correlation between serum PSA and bone scintigraphy in patients with newly diagnosed untreated PCa has been further investigated (62). Results suggest that a staging bone scan may be superfluous if the serum PSA concentration is less than 20 ng/mL in asymptomatic patients with well or moderately differentiated (up to 7: 3+4) tumours. In contrast, in patients with poorly differentiated tumours and locally advanced disease, a staging bone scan should be obtained irrespective of the serum PSA value (63).

7.4 Guidelines for the diagnosis and staging of PCa

Diagnosis of PCa - Conclusions
An abnormal DRE result or elevated serum PSA measurement could indicate PCa. The exact cut-off level of what is considered to be a normal PSA value has yet to be determined, but values of approximately < 2-3 ng/mL are often used for younger men.
The diagnosis of PCa depends on histopathological (or cytological) confirmation.
Staging of PCa - Conclusions
Despite its high specificity in the evaluation of EPE and SVI, TRUS has low sensitivity and a tendency to understage PCa. Even with the advent of colour power Doppler and contrast enhancement the accuracy of TRUS in local staging remains inadequate and largely operator-depended. In comparison with DRE, TRUS and CT, MRI demonstrates higher accuracy for the assessment of uni- or bi-lobar disease (T2), EPE and SVI (T3), as well as the invasion of adjacent structures (T4).
Currently only sentinel lymph node dissection or extended PLND allow for histological detection of lymph node metastases with high sensitivity.

Diagnosis of PCa - Recommendations		**GR**
Biopsy and further staging investigations are only indicated if they affect the management of the patient.		C
	Transrectal ultrasound (TRUS)-guided systemic biopsy is the recommended method in most cases of suspected PCa. A minimum of 8 systemic, laterally directed, cores are recommended, with perhaps more cores in larger volume prostates.	B
	Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates.	C
	One set of repeat biopsies is warranted in cases with persistent indication for PCa (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at the initial biopsy).	B
	Overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient.	C
Transrectal peri-prostatic injection with a local anaesthetic can be offered to patients as effective analgesia when undergoing prostate biopsies.		A
Staging of PCa - Recommendations		
Local staging (T-staging) of PCa should be based on MRI. Further information is provided by the number and sites of positive prostate biopsies, the tumour grade, and the level of serum PSA.		C
For local staging TRUS should not be used since it has low sensitivity and a tendency to understage PCa.		
	Lymph node status (N-staging) need only be assessed when potentially curative treatment is planned. Patients with stage T2 or less, PSA < 20 ng/mL and a Gleason score ≤ 6 have a lower than 10% likelihood of having node metastases and can be spared nodal evaluation.	B
	In clinically localised PCa, staging must be done by pelvic lymph node dissection since it presents the only reliable staging method, given the significant limitations of pre-operative imaging in the detection of small metastases (< 5 mm).	
Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if the serum PSA level is < 20 ng/mL in the presence of well or moderately differentiated tumours.		B
In equivocal cases, ^{11}C-choline-, ^{18}F-flouride-PET/CT or whole body MRI are an option.		C

CT = computed tomography; DCE-MRI = dynamic contrast-enhanced MRI; DRE = digital rectal examination; EPE = extraprostatic extension; MRI = magnetic resonance imaging; MRSI = magnetic resonance spectroscopic imaging; PCa = prostate cancer; PET = positron emission tomography; PLND = pelvic lymph-node dissection; PSA = prostate-specific antigen; SVI = seminal vesicle invasion; TRUS = transrectal ultrasound.

7.5 References

1. Spigelman SS, McNeal JE, Freiha FS, et al. Rectal examination in volume determination of carcinoma of the prostate: clinical and anatomical correlations. J Urol 1986 Dec;136(6):1228-30. http://www.ncbi.nlm.nih.gov/pubmed/3773095
2. Partin AW, Carter HB, Chan DW, et al. Prostate specific antigen in the staging of localized prostate cancer: influence of tumour differentiation, tumour volume and benign hyperplasia. J Urol 1990 Apr;143(4):747-52. http://www.ncbi.nlm.nih.gov/pubmed/1690309
3. Partin AW, Mangold LA, Lamm DM, et al. Contemporary update of the prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology 2001 Dec;58(6):843-8. http://www.ncbi.nlm.nih.gov/pubmed/11744442
4. Morote J, Encabo G, de Torres IM. Use of percent free prostate-specific antigen as a predictor of the pathological features of clinically localized prostate cancer. Eur Urol 2000 Aug;38(2):225-9. http://www.ncbi.nlm.nih.gov/pubmed/10895016
5. Custovic Z, Kraus O, Tomaskovic I, et al. Serum tPSA, cPSA, related density parameters and chromogranin A as predictors of positive margins after radical prostatectomy. Anticancer Res 2007 Jul-Aug;27(4C):2817-21. http://www.ncbi.nlm.nih.gov/pubmed/17695453
6. Smith JA Jr, Scardino PT, Resnick MI, et al. Transrectal ultrasound versus digital rectal examination for the staging of carcinoma of the prostate: results of a prospective multi-institutional trial. J Urol 1997 Mar;157(3):902-6. http://www.ncbi.nlm.nih.gov/pubmed/9072596
7. Liebross RH, Pollack A, Lankford SP, et al. Transrectal ultrasound for staging prostate carcinoma prior to radiation therapy: an evaluation based on disease outcome. Cancer 1999 Apr;85(7):1577-85. http://www.ncbi.nlm.nih.gov/pubmed/10193949
8. Hsu CY, Joniau S, Oyen R, et al. Detection of clinical unilateral T3a prostate cancer - by digital rectal examination or transrectal ultrasonography? BJU Int 2006 Nov;98(5):982-5. http://www.ncbi.nlm.nih.gov/pubmed/16945120
9. Mitterberger M, Pinggera GM, Pallwein L, et al. The value of three-dimensional transrectal ultrasonography in staging prostate cancer. BJU Int 2007 Jul;100(1):47-50. http://www.ncbi.nlm.nih.gov/pubmed/17433033
10. Sauvain JL, Palascak P, Bourscheid D, et al. Value of power Doppler and 3D vascular sonography as a method for diagnosis and staging of prostate cancer. Eur Urol 2003 Jul;44(1):21-30; discussion 30-1. http://www.ncbi.nlm.nih.gov/pubmed/12814671
11. Zalesky M, Urban M, Smerhovský Z, et al. Value of power Doppler sonography with 3D reconstruction in preoperative diagnostics of extraprostatic tumor extension in clinically localized prostate cancer. Int J Urol 2008;15(1):68-75; discussion 75. http://www.ncbi.nlm.nih.gov/pubmed/18184177
12. Smeenge M, Mischi M, Laguna Pes MP, et al. Novel contrast-enhanced ultrasound imaging in prostate cancer.World J Urol. 2011 Oct;29(5):581-7. http://www.ncbi.nlm.nih.gov/pubmed/21847656
13. Saliken JC, Gray RR, Donnelly BJ, et al. Extraprostatic biopsy improves the staging of localized prostate cancer. Can Assoc Radiol J 2000 Apr;51(2):114-20. http://www.ncbi.nlm.nih.gov/pubmed/10786920
14. Stone NN, Stock RG, Unger P. Indications for seminal vesicle biopsy and laparoscopic pelvic lymph node dissection in men with localized carcinoma of the prostate. J Urol 1995 Oct;154(4):1392-6. http://www.ncbi.nlm.nih.gov/pubmed/7658545
15. Allepuz Losa CA, Sans Velez JI, Gil Sanz MJ, et al. Seminal vesicle biopsy in prostate cancer staging. J Urol 1995 Oct;154(4):1407-11. http://www.ncbi.nlm.nih.gov/pubmed/7544842
16. Guillonneau B, Debras B, Veillon B, et al. Indications for preoperative seminal vesicle biopsies in staging of clinically localized prostatic cancer. Eur Urol 1997;32(2):160-5. http://www.ncbi.nlm.nih.gov/pubmed/9286646
17. Freedland SJ, Csathy GS, Dorey F, et al. Percent prostate needle biopsy tissue with cancer is more predictive of biochemical failure or adverse pathology after radical prostatectomy than prostate specific antigen or Gleason score. J Urol 2002 Feb;167(2 PT 1):516-20. http://www.ncbi.nlm.nih.gov/pubmed/11792909

18. Quinn DI, Henshall SM, Brenner PC, et al. Prognostic significance of preoperative factors in localized prostate carcinoma treated with radical prostatectomy: importance of percentage of biopsies that contain tumor and the presence of biopsy perineural invasion. Cancer 2003 Apr;97(8):1884-93. http://www.ncbi.nlm.nih.gov/pubmed/12673714
19. Elliott SP, Shinohara K, Logan SL, et al. Sextant prostate biopsies predict side and sextant site of extracapsular extension of prostate cancer. J Urol 2002 Jul;168(1):105-9. http://www.ncbi.nlm.nih.gov/pubmed/12050501
20. Narayan P, Gajendran V, Taylor SP, et al. The role of transrectal ultrasound-guided biopsy-based staging, preoperative serum prostate-specific antigen, and biopsy Gleason score in prediction of final pathological diagnosis in prostate cancer. Urology 1995 Aug;46(2):205-12. http://www.ncbi.nlm.nih.gov/pubmed/7542823
21. Barqawi AB, Rove KO, Gholizadeh S, ET AL. The role of 3-dimensional mapping biopsy in decision making for treatment of apparent early stage prostate cancer. J Urol 2011 Jul;186(1):80-5. http://www.ncbi.nlm.nih.gov/pubmed/21571335
22. Lee N, Newhouse JH, Olsson CA, Benson MC, et al. Which patients with newly diagnosed prostate cancer need a computed tomography scan of the abdomen and pelvis? An analysis based on 588 patients. Urology 1999 Sep;54(3):490-4. http://www.ncbi.nlm.nih.gov/pubmed/10475360
23. Jager GJ, Severens JL, Thornbury JR, et al. Prostate cancer staging: should MR imaging be used? A decision analytic approach. Radiology 2000 May;215(2):445-51. http://www.ncbi.nlm.nih.gov/pubmed/10796923
24. Masterson TA, Touijer K. The role of endorectal coil MRI in preoperative staging and decision-making for the treatment of clinically localized prostate cancer. MAGMA 2008 Nov;21(6):371-7. http://www.ncbi.nlm.nih.gov/pubmed/18751745
25. Heijmink SW, Fütterer JJ, Hambrock T, et al. Prostate cancer: body-array versus endorectal coil MR imaging at 3 T - comparison of image quality, localization, and staging performance. Radiology 2007;244(1):184-95. http://www.ncbi.nlm.nih.gov/pubmed/17495178
26. Mullerad M, Hricak H, Kuroiwa K, et al. Comparison of endorectal magnetic resonance imaging, guided prostate biopsy and digital rectal examination in the preoperative anatomical localization of prostate cancer. J Urol 2005 Dec;174(6):2158-63. http://www.ncbi.nlm.nih.gov/pubmed/16280755
27. Sala E, Akin O, Moskowitz CS, et al. Endorectal MR imaging in the evaluation of seminal vesicle invasion: diagnostic accuracy and multivariate feature analysis. Radiology 2006 Mar;238(3):929-37. http://www.ncbi.nlm.nih.gov/pubmed/16424250
28. Wang L, Mullerad M, Chen HN, et al. Prostate cancer: incremental value of endorectal MRI findings for prediction of extracapsular extension. Radiology 2004 Jul;232(1):133-9. http://www.ncbi.nlm.nih.gov/pubmed/15166321
29. Hricak H, Wang L, Wei DC, et al. The role of preoperative endorectal MRI in the decision regarding whether to preserve or resect neurovascular bundles during radical retropubic prostatectomy. Cancer 2004 Jun;100(12):2655-63. http://www.ncbi.nlm.nih.gov/pubmed/15197809
30. Wang L, Hricak H, Kattan MW, et al. Prediction of seminal vesicle invasion in prostate cancer: incremental value of adding endorectal MRI to the Kattan Nomogram. Radiology 2007 Jan;242(1): 182-8. http://www.ncbi.nlm.nih.gov/pubmed/17090712
31. Wang L, Hricak H, Kattan MW, et al. Prediction of organ confined prostate cancer: incremental value of MRI and MRI sprectroscopic imaging to staging nomograms. Radiology 2006;238(2):597-603. http://www.ncbi.nlm.nih.gov/pubmed/16344335
32. Fuchsjager M, Shukla-Dave A, Akin O, et al. Prostate cancer imaging. Acta Radiol 2008;49(1):107-20. http://www.ncbi.nlm.nih.gov/pubmed/18210320
33. Scheidler J, Hricak H, Vigneron DB, et al. Prostate cancer: localization with three-dimensional proton MR spectroscopic imaging - clinicopathologic study. Radiology 1999;213(2):473-80. http://www.ncbi.nlm.nih.gov/pubmed/10551229
34. Zakian KL, Sircar K, Hricak H, et al. Correlation of proton MR spectroscopic imaging with Gleason score based on step section pathologic analysis after radical prostatectomy. Radiology 2005;234(3):804-14. http://www.ncbi.nlm.nih.gov/pubmed/15734935

35. Rinnab L, Blumstein NM, Mottaghy FM, et al. ^{11}C-choline positron-emission tomography/computed tomography and transrectal ultrasonography for staging localized prostate cancer. BJU Int 2007 Jun;99(6):1421-6.
http://www.ncbi.nlm.nih.gov/pubmed/17355373
36. Stone NN, Stock RG, Parikh D, et al. Perineural invasion and seminal vesicle involvement predict pelvic lymph node metastasis in men with localized carcinoma of the prostate. J Urol 1998 Nov;160(5):1722-6.
http://www.ncbi.nlm.nih.gov/pubmed/9783940
37. Pisansky TM, Zincke H, Suman VJ, et al. Correlation of pretherapy prostate cancer characteristics with histologic findings from pelvic lymphadenectomy specimens. Int J Radiat Oncol Biol Phys 1996 Jan;34(1):33-9.
http://www.ncbi.nlm.nih.gov/pubmed/12118563
38. Cagiannos I, Karakiewicz P, Eastham JA, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. J Urol 2003 Nov;170(5):1798-803.
http://www.ncbi.nlm.nih.gov/pubmed/14532779
39. Haese A, Epstein JI, Huland H, et al. Validation of a biopsy-based pathologic algorithm for predicting lymph node metastases in patients with clinically localized prostate carcinoma. Cancer 2002 Sep;95(5):1016-21.
http://www.ncbi.nlm.nih.gov/pubmed/12209685
40. Hoivels AM, Heesakkers RAM, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clinical Radiology 2008;63:387-95.
http://www.ncbi.nlm.nih.gov/pubmed/18325358
41. Jager GJ, Barentsz JO, Oosterhof GO, et al. Pelvic adenopathy in prostatic and urinary bladder carcinoma: MR-imaging with a three-dimensional T1-weighted magnetization-prepared-rapid gradient-echo sequence. Am J Roentgenol 1996 Dec;167(6):1503-7.
http://www.ncbi.nlm.nih.gov/pubmed/8956585
42. Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 2003 Jun;348(25):2491-9.
http://www.ncbi.nlm.nih.gov/pubmed/12815134
43. Heesakkers RA, Fütterer JJ, Hövels AM, et al. Prostate cancer evaluated with ferumoxtran-10-enhanced T2*-weighted MR imaging at 1.5 and 3.0 T: early experience. Radiology 2006 May; 239(2):481-7.
http://www.ncbi.nlm.nih.gov/pubmed/16641354
44. Salminen E, Hogg A, Binns D, et al. Investigations with FDG-PET scanning in prostate cancer show limited value for clinical practice. Acta Oncol 2002;41(5):425-9.
http://www.ncbi.nlm.nih.gov/pubmed/12442917
45. Husarik DB, Miralbell R, Dubs M, et al. Evaluation of [(18)F]-choline PET/CT for staging and restaging of prostate cancer. Eur J Nucl Med Mol Imaging 2008 Feb;35(2):253-63.
http://www.ncbi.nlm.nih.gov/pubmed/17926036
46. Schiavina R, Scattoni V, Castellucci P, et al. (11)C-choline positron emission tomography/computerized tomography for preoperative lymph-node staging in intermediate-risk and high-risk prostate cancer: comparison with clinical staging nomograms. Eur Urol 2008 Aug;54(2):392-401.
http://www.ncbi.nlm.nih.gov/pubmed/18456393
47. Heidenreich A, Varga Z, Von Knobloch R. Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: high incidence of lymph node metastasis. J Urol 2002 Apr;167(4):1681-6.
http://www.ncbi.nlm.nih.gov/pubmed/11912387
48. Bader P, Burkhard FC, Markwalder R, et al. Is a limited lymph node dissection an adequate staging procedure for prostate cancer? J Urol 2002 Aug;168(2):514-18, discussion 518.
http://www.ncbi.nlm.nih.gov/pubmed/12131300
49. Weckermann D, Dorn R, Holl G, et al. Limitations of radioguided surgery in high-risk prostate cancer. Eur Urol 2007 Jun;51(6):1549-56.
http://www.ncbi.nlm.nih.gov/pubmed/16996201
50. Weckermann D, Dorn R, Trefz M, et al. Sentinel lymph node dissection for prostate cancer: experience with more than 1,000 patients. J Urol 2007 Mar;177(3):916-20.
http://www.ncbi.nlm.nih.gov/pubmed/17296375
51. Whitmore WF Jr. Natural history and staging of prostate cancer. Urol Clin North Am 1984 May;11(2): 205-20.
http://www.ncbi.nlm.nih.gov/pubmed/6375067

52. Wolff JM, Ittel TH, Borchers H, et al. Metastatic workup of patients with prostate cancer employing alkaline phosphatase and skeletal alkaline phosphatase. Anticancer Res 1999 Jul-Aug;19(4A):2653-5. http://www.ncbi.nlm.nih.gov/pubmed/10470213
53. Lorente JA, Morote J, Raventos C, et al. Clinical efficacy of bone alkaline phosphatase and prostate specific antigen in the diagnosis of bone metastasis in prostate cancer. J Urol 1996 Apr;155(4):1348-51. http://www.ncbi.nlm.nih.gov/pubmed/8632571
54. Lorente JA, Valenzuela H, Morote J, et al. Serum bone alkaline phosphatase levels enhance the clinical utility of prostate specific antigen in the staging of newly diagnosed prostate cancer patients. Eur J Nucl Med 1999 Jun;26(6):625-32. http://www.ncbi.nlm.nih.gov/pubmed/10369948
55. McGregor B, Tulloch AG, Quinlan MF, et al. The role of bone scanning in the assessment of prostatic carcinoma. Br J Urol 1978 May;50(3):178-81. http://www.ncbi.nlm.nih.gov/pubmed/753456
56. O'Donoghue EP, Constable AR, Sherwood T, et al. Bone scanning and plasma phosphatases in carcinoma of the prostate. Br J Urol 1978 May;50(3):172-7. http://www.ncbi.nlm.nih.gov/pubmed/753455
57. Buell U, Kleinhans E, Zorn-Bopp E, et al. A comparison of bone imaging with Tc-99m DPD and Tc-99m MDP: concise communication. J Nucl Med 1982 Mar;23(3):214-17. http://www.ncbi.nlm.nih.gov/pubmed/6460854
58. Even-Sapir E, Metser U, Mishani E, et al. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multifield-of-view SPECT, ^{18}F-fluoride PET/CT. J Nucl Med 2006 Feb;47(2):287-97. http://www.ncbi.nlm.nih.gov/pubmed/16455635
59. Beheshti M, Vali R, Langsteger W. [^{18}F]Fluorocholine PET/CT in the assessment of bone metastases in prostate cancer. Eur J Nucl Med Mol Imaging 2007 Aug;34(8):1316-7. http://www.ncbi.nlm.nih.gov/pubmed/17476505
60. Bouchelouche K, Oehr P. Recent developments in urologic oncology: positron emission tomography molecular imaging. Curr Opin Oncol 2008 May;20(3):321-6. http://www.ncbi.nlm.nih.gov/pubmed/18391633
61. Rana A, Karamanis K, Lucas MG, et al. Identification of metastatic disease by T category, Gleason score and serum PSA level in patients with carcinoma of the prostate. Br J Urol 1992 Mar;69(3): 277-81. http://www.ncbi.nlm.nih.gov/pubmed/1373666
62. Lee N, Fawaaz R, Olsson CA, et al. Which patients with newly diagnosed prostate cancer need a radionuclide bone scan? An analysis based on 631 patients. Int J Radiat Oncol Biol Phys 2000 Dec;48(5):1443-6. http://www.ncbi.nlm.nih.gov/pubmed/11121646
63. Bruwer G, Heyns CF, Allen FJ. Influence of local tumour stage and grade on reliability of serum prostate-specific antigen in predicting skeletal metastases in patients with adenocarcinoma of the prostate. Eur Urol 1999;35(3):223-7. http://www.ncbi.nlm.nih.gov/pubmed/10072624

8. TREATMENT: DEFERRED TREATMENT (WATCHFUL WAITING/ACTIVE MONITORING)

8.1 Introduction

There is a great difference between the incidence of PCa and deaths from PCa. In 2007, in the USA, there were 240,890 new cases with only 33,720 deaths (1). Several autopsy studies of people dying from different causes have shown that while 60-70% of older men have histological PCa (2), a large proportion of these tumours will not progress. Prostate cancer is diagnosed in only 15-20% of men during their lifetime, with a 3% lifetime risk of death (3).

The incidence of small, localised, well-differentiated PCa is increasing, mainly as a result of prostate-specific antigen (PSA) screening and 'multicore' schemes of prostate biopsy. These data suggest that many men with localised PCa would not actually benefit from definitive treatment. With the aim of reducing the risk of overtreatment in this subgroup of patients, two conservative management strategies of 'watchful waiting' and 'active surveillance' have been proposed.

8.1.1 *Definition*

8.1.1.1 *Watchful waiting (WW)*

Watchful waiting is also known as 'deferred treatment' or 'symptom-guided treatment'. This term was coined in the pre-PSA screening era (before 1990) and referred to the conservative management of PCa until the development of local or systemic progression. At this point, the patient would then be treated palliatively with transurethral resection of the prostate (TURP) or other procedures for urinary tract obstruction, and hormonal therapy or radiotherapy for the palliation of metastatic lesions.

8.1.1.2 *Active surveillance (AS)*

Active surveillance is also known as 'active monitoring'. It is the new term for the conservative management of PCa. Introduced in the past decade, it includes an active decision not to treat the patient immediately. Instead, the patient is followed up under close surveillance and treated at pre-defined thresholds that classify progression (i.e. short PSA doubling time and deteriorating histopathological factors on repeat biopsy). The treatment options are intended to be curative.

8.2 Deferred treatment of localised PCa (stage T1-T2, Nx-N0, M0)

8.2.1 *Watchful waiting*

The rationale behind WW is the observation that PCa often progresses slowly, and is diagnosed in older men, in whom there is a high incidence of co-morbidity and related high competitive mortality (4). Watchful waiting can be considered as an option for treating patients with localised PCa and a limited life expectancy or for older patients with less aggressive cancers.

There have been several attempts to summarise the key papers dealing with deferred treatment in patients with presumed localised PCa (5-7). Most have presented the same results, as they analyse roughly the same series, but using somewhat different methodologies. The outcome studies in WW usually included patients, whose PSA readings were not always available and who had predominantly palpable lesions that would currently be defined as intermediate-risk tumours (8). The most recent study used data from the PSA era of the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute in the USA (9). These studies included patients with a follow-up of up to 25 years, for whom the endpoints are overall survival (OS) and disease-specific survival (DSS).

Several WW series show a very consistent DSS ratio at 10 years, ranging from 82-87% (5,10-14), and up to 80-95% if T1-T2 Gleason ≤ 7 (9). In three studies with data beyond 15 years, the DSS was 80%, 79% and 58%, respectively (11,13,14). Two of them reported a 20-year DSS of 57% and 32%, respectively (11,13).

Chodak et al. reported a pooled analysis of the original data from 828 patients treated by WW (5). The paper was based on patients from six non-randomised studies and described cancer-specific survival and metastasis-free survival after 5 and 10 years of follow-up (5) (LE: 2b).

Tumour grade is clearly significant, with very low survival rates for grade 3 tumours. Although the 10-year cancer-specific rate is equally good (87%) for grade 1 and 2 tumours, the latter have a significantly higher progression rate, with 42% of these patients developing metastases (Table 9).

Table 9: Outcome of deferred treatment in localised PCa in relation to tumour grade (6): percentage of patients (95% confidence interval) surviving at 5 and 10 years

Grade	5 years (%)	10 years (%)
Disease-specific survival		
Grade 1	98 (96-99)	87 (81-91)
Grade 2	97 (93-98)	87 (80-92)
Grade 3	67 (51-79)	34 (19-50)
Metastasis-free survival		
Grade 1	93 (90-95)	81 (75-86)
Grade 2	84 (79-89)	58 (49-66)
Grade 3	51 (36-64)	26 (13-41)

The importance of tumour grade on survival after conservative management of PCa was also underlined in a large register study using the SEER database (9) (LE: 3). Patients with grade 1, 2 and 3 tumours had 10-year cancer-specific survival rates of 91%, 90% and 74%, respectively, correlating with data from the pooled analysis.

The paper by Chodak et al. also specifically described the outcome for stage T1a patients (5), with cancer-specific 10-year survival rates of 96% and 94%, respectively, for grade 1 and 2 tumours. The metastasis-free survival rate was 92% for patients with grade 1 tumours, but 78% for those with grade 2

tumours, indicating a higher risk of progression in individuals with moderately differentiated tumours. This difference in progression rate correlates with other studies on stage T1a disease (15,16).

The impact of grade on the risk of tumour progression and ultimately death from PCa was also described in a paper by Albertsen et al. in the pre-PSA era (17). The study re-evaluated all biopsy specimens using the more widely accepted Gleason score, and showed that the risk of PCa death was very high in Gleason 7-10 tumours, intermediate in Gleason 6 tumours, but low in Gleason 2-5 cancers (Table 10) (18,19) (LE: 3).

This paper also showed that Gleason 6-10 tumours carry a continuously increasing risk of ending the patient's life for up to 15 years of follow-up after conservative management. The cancer-specific survival curves for this group of patients have been published in a recent discussion article on different methods of assessing outcome in treatment for localised PCa (18).

Table 10: The 15-year risk of dying from PCa in relation to Gleason score at diagnosis in patients with localised disease aged 55-74 years (17,18)

Gleason score	Risk of cancer death* (%)	Cancer-specific mortality† (%)
2-4	4-7	8
5	6-11	14
6	18-30	44
7	42-70	76
8-10	60-87	93

** The figures on the risk of cancer death differ for different age groups and represent the true risk in the studied population (taking actual competing mortality from other causes into consideration).*
† The cancer-specific mortality compensates for differences in competing mortality and indicates the outcome if the patient actually lived for 15 years.

Three randomised clinical trials have reported long-term follow-up of patients randomised to WW or radical prostatectomy: the first was in the pre-PSA screening era (19); the second was at the beginning of PSA screening (20); and the third was a recent study, the results of which have been published in 2012 (21).

Between 1967 and 1975, the Veterans Administration Cooperative Urological Research Group randomised 142 patients affected by clinical localised PCa. The study was underpowered to detect treatment differences (22).

Between 1989 and 1999, the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomised 695 patients with clinical stage T1-T2 to WW (n = 348) or radical prostatectomy (n = 347) (Table 11) (30). This study began after PSA screening was introduced into clinical practice, but only 5% of men were diagnosed by screening. After a median follow-up of 12.8 years, this study showed a significant decrease in cancer-specific mortality, overall mortality, metastatic risk progression and local progression in patients treated with radical prostatectomy versus WW (LE: 1b).

Table 11: Outcome of Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) at 15 years of follow-up (median of 12.8 years) (20)

	RP (N = 347) % (n)	WW (N = 348) % (n)	Relative risk (95% CI)	p value
Disease-specific mortality	14.6	20.7	0.62	0.01
Overall mortality	46.1	57.2	0.75 (0.61-0.92)	0.007
Metastatic progression	21.7	33.4	0.59 (0.45-0.79)	< 0.001
Local progression	21.5	49.3	0.34 (0.26-0.45)	

RP = radical prostatectomy; WW = watchful waiting.

Subgroup analysis showed that the overall difference was not modified by PSA level (below or above 10 ng/mL) or by the Gleason score (below 7 or above) at the time of diagnosis. However, age at that the time of randomisation had a profound impact, the benefit on overall survival and metastases free survival being only seen for those below 65 years of age.

The Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT) recruited 731 men with clinically organ confined prostate cancer to the arms of radical prostatectomy or WW (21). Inclusion criteria were clinically organ confined PCa (cT1-2cN0cM0) with a PSA < 50 ng/mL,

patient age < 75 years and a life expectancy > 10 years. It has to be considered that 50% of the men had a non-palpable PCa, which was only the case in 12% of the patients in the SPCG-4 trial (20). Both prostate biopsy and radical prostatectomy specimens were pathohistologically assessed by a reference pathologist.

After a mean follow-up of 10 years, no statistically significant between both treatment arms could be demonstrated with regard to overall mortality (47% versus 49.9%, p = 0.22) and PCa-specific survival (5.8% versus 8.4%, p = 0.09). There were also no statistically significant differences concerning overall survival between both treatment groups when considering patient age, Gleason Score, performance status, and Charlson comorbidity score. Only patients exhibiting a pre-treatment PSA serum concentration > 10 ng/ml or high risk PCa experienced a statistically significant benefit concerning overall survival with a relative risk reduction of mortality of 33% (p = 0.02) and 31% (p < 0.01), respectively. In the pooled analysis a relative risk reduction and an absolute risk reduction of 31% and 10.5%, respectively, was identified for patients with intermediate/high risk PCa (p < 0.01) Patients who underwent radical prostatectomy also experienced a statistically significant reduction concerning the development of bone metastases (4.7% versus 10.6%, p < 0.01).

No data are available comparing WW and radiotherapy. Some data are available for hormonal treatment. For patients who choose deferred treatment, there appears to be a modest risk of disease progression, although shorter cancer-specific survival times have been reported after deferred therapy compared with immediate hormone therapy, in presumed localised PCa (not using PSA for staging) after 15 years of follow-up (22). In contrast to Lundgren et al. (22), the report of the Casodex Early Prostate Cancer Trialists' Group programme showed a higher mortality in a group of men with localised PCa treated with bicalutamide, 150 mg/day, than in those who received placebo (23).

Conclusions on deferred treatment	**LE**
Clinical stage T1c currently represents 40-50% of new cases of PCa (24). The incidence of small, localised, well-differentiated PCa is increasing, mainly as a result of PSA screening and 'multicore' schemes of prostate biopsy.	
The SPCG-4 study demonstrated significant advantages for RP over WW, but only 5% of those studied were PSA-screened patients.	1b
During the past 20 years, there appears to have been a shift towards higher Gleason scoring levels (25), even in cases evaluating microscopic foci of PCa. Some tumours previously given a Gleason score of 6 (3 + 3) might be scored today as 7 (3 + 4) or higher.	3
The lead time in PSA screening is about 10 years (26,27). It is therefore possible that cancer-related mortality from untreated, non-screen-detected PCa in patients with contemporary Gleason scores of 6 might be as low as 10% at 20-year follow-up (28).	2a
The comparison of immediate hormonal treatment to WW in localised PCa remain controversial and may be associated with an increased mortality with bicalutamide.	2a

It appears that many small localised well-differentiated tumours will not progress, and radical therapy may lead to substantial overtreatment with resulting effects on the patients' quality of life and treatments costs. This has been further confirmed by a recent analysis at 5 and 10 years of 19,639 patients > 65 years from the SEER database not given curative treatment. Based on comorbidities (Charlson score), most men with a Charlson score ≥ 2 died from competing causes at 10 years, whatever their initial age (below or above 65 years). However, men with no or just one comorbidity had a low risk of death at 10 years, especially for well or moderately differentiated lesions (29). In men with a Charlson score ≥ 2, tumour aggressiveness had little impact on overall survival, suggesting that perhaps these patients could have been spared the biopsies and diagnosis of cancer. This strengthens the major role of initial comorbidity evaluation, leading to an individual survival probability, before embarking an individual on any form of medical intervention such as biopsies or treatment (30).

*8.2.2 **Active surveillance***

Active surveillance was conceived with the aim of reducing the ratio of overtreatment in patients with clinically confined very low-risk PCa, without giving up radical treatment, as happens with WW. Currently, the only data available is data from non-mature randomised clinical trials of active surveillance, with a follow-up of less than 10 years. Active surveillance can therefore only be proposed for highly selected low-risk patients, particularly as the data indicate there is a significant risk of tumour progression after conservative treatment for some patients with apparently localised PCa. This conclusion is also supported by other studies, which have shown that patients with a life expectancy > 10 years have a higher mortality rate from PCa in the absence of curative treatment. These studies include the Johansson series, which showed that there is a higher risk of dying from PCa in patients surviving more than 15 years with well- and moderately differentiated tumours at diagnosis

(31) (LE: 3). In the light of these findings, it is essential that a more precise selection of candidates for active surveillance is carried out.

A multicentre clinical trial of active surveillance versus immediate treatment was opened in the USA in 2006. Its results are expected in 2025. Choo, Klotz and co-workers were the first to report on a prospective active surveillance protocol (32,33). The most advanced cohort to date was reported last year by Klotz (43). A total of 450 patients with clinical stage T1c or T2a, PSA ≤ 10 ng/mL were enrolled with an overall Gleason score ≤ 6 (PSA ≤ 15), with patients > 70 years having a Gleason score ≤ 7 (3 + 4). Initially, six biopsies were performed, followed by the usual extended 12-core protocol during the study. At a median follow-up of 6.8 years, the 10-year overall survival was 68%. At 10 years, the disease-specific survival was 97.2%, with 62% of men still alive on active surveillance. Subsequently, 30% of patients underwent a radical treatment for the following reasons: 48% for a PSA doubling time < 3 years; 27% for Gleason score progression on repeat biopsies; and 10% because of patient preference.

A variety of additional studies on active surveillance in clinically organ confined disease (Tables 12 and 13) have now been published. All have confirmed that, in well-selected patients with very low-risk disease, there was a very low rate of progression and cancer-specific death, with only a few patients required delayed radical intervention. However, an extended follow-up is necessary to obtain definitive results. Thus, active surveillance might mean no treatment at all for patients older than 70 years, while in younger patients, it might mean a possible treatment delayed for years. The repeated biopsies that are part of active surveillance might then become important for their potential side effect on nerve preservation if surgery is subsequently considered.

Table 12: Clinical trials of AS for organ-confined PCa: inclusion criteria

	N	**Median age**	**Criteria**
Dall'Era (35)	321	64	Gleason ≤ 3+3, PSAd ≤ 0.15 ng/mL, T1-T2a, ≤ 33% biopsies+, ≤ 50% cores
Van den Berg (36)	616	66	Gleason ≤ 3+3, PSA ≤ 10 ng/mL, PSAd ≤ 0,2 ng/mL, T1C-T2, ≤ 2 biopsies +
Van As (37)	326	67	Gleason ≤ 3+4, PSA < 15 ng/mL, T1-T2a,N0Nx,M0MX ≤ T2a, ≤ 50% biopsies +
Soloway (38)	230	64	Gleason ≤ 6, PSA ≤ 10 ng/dL, T1a-T2, ≤ 2 biopsies+, ≤ 20% cores +
Klotz (34)	453	70	Gleason ≤ 6, PSA ≤ 10 ng/mL, (up to 1999: Gleason ≤ 3+4, PSA ≤ 15 ng/mL) < 3 biopsies +, < 50% each core
Tosoain (39)	769	66	Gleason ≤ 3+3, PSAd ≤ 0.15 ng/mL, T1, ≤ 2 biopsies+, ≤ 50% cores
Adamy (40)	238	64	Gleason ≤ 3+3, PSA ≤ 10 ng/mL, T1-T2a, ≤ 3 biopsies+, ≤ 50% cores

Table 13: Clinical trials of AS for organ-confined PCa: main results

		Progression		RP (%)	Survival (%)		
	Median follow-up (months)	Biopsy (%)	PSA / PSA DT	Patient's request	OS	CSS	PFS
Dall'Era	47	35	5	8	97	100	54
Van den Berg	52	-	13	18	91	100	68
Van As	22	13	18	2	98	100	73
Soloway	32	10	-	-	100	100	86
Klotz	82	9	14	3	78.6	97.2	70
Tosoain	32	14	-	9	98	100	54
Adamy	22	13	14	11	-	-	-

OS = overall survival: CSS = cancer-specific survival; PFS =progression-free survival.

Different series have identified several eligibility criteria for enrolment (41):

- clinically confined PCa (T1-T2);
- Gleason score < 7 for most studies;
- PSA < 10-15 ng/mL.

Limited tumour volume is defined by a low number of involved cores and a low tumour length on each involved core. The role of other tools. e.g. MRI, to better define acceptable lesions remains controversial, except

probably for anterior lesions (42). The PCA3 level may become a practical tool in the future (43).
Active surveillance is based on repeated DRE, PSA and most importantly repeated biopsies, usually every year. The place of early repeated biopsy has become an important part of the selection process, based on the risk of under-detection of grade 4 (35,40,44,45).
The criteria for active treatment are less well defined (5), but most groups have used:

- PSA doubling time with a cut-off value ranging between ≤ 2 and ≤ 4 years. This criterion is becoming questionable because of a weak link between PSA doubling time and grade progression on repeated biopsy (46).
- Gleason score progression to ≥ 7 during follow-up systematic biopsies, at intervals ranging from 1-4 years.
- Patient's request mainly based on anxiety. This is a significant factor (36) and might affect up to 10% of treated patients. No data is available regarding active surveillance. However, data from the SPCG-4 trial has suggested that, based on self-administered questionnaires 87% of the included patients, the treatment group always reported inferior well-being, depression and psychological status, but this difference was never significant (47).

8.3 Deferred treatment for locally advanced PCa (stage T3-T4, Nx-N0, M0)

The literature reporting on deferred treatment for locally advanced PCa is sparse. There are no randomised studies that compare more aggressive treatments, such as radiotherapy or surgery, with or without hormones.

Most patients whose disease progresses after deferred treatment of locally advanced PCa will be candidates for hormone therapy. There are reports from non-randomised studies showing that hormone treatment may safely be delayed until metastatic progression occurs, as no survival advantage was noted between patients treated with immediate orchiectomy compared with delayed treatment (48,49).

In a prospective randomised clinical phase III trial (EORTC 30981), 985 patients with T0-4 N0-2 M0 PCa were randomly assigned to immediate androgen-deprivation therapy (ADT) or received ADT only on symptomatic disease progression or occurrence of serious complications (50,51). After a median follow-up of 7.8 years, the overall survival hazard ratio was 1.25 (95% confidence interval [CI]: 1.05-1.48; non-inferiority $p > 0.1$) favouring immediate treatment, seemingly due to fewer deaths of non-prostatic cancer causes ($p = 0.06$). The time from randomisation to progression of hormone-refractory disease did not differ significantly nor did prostate cancer-specific survival. The median time to the start of deferred treatment after study entry was 7 years. In this group, 126 patients (25.6%) died without ever needing treatment (44% of deaths in this arm). The conclusion drawn from this study is that immediate ADT resulted in a modest but statistically significant increase in overall survival, but no significant difference in PCa mortality or symptom-free survival. This raises the question of the usefulness of such a small statistical benefit.

Furthermore, the authors identified significant risk factors associated with a significantly worse outcome: in both arms. Patients with a baseline PSA > 50 ng/mL were at a > 3.5-fold higher risk of dying of PCa than patients with a baseline PSA ≤ to 8 ng/mL. If the baseline PSA was between 8 ng/mL and 50 ng/mL, the risk of PCa death was approximately 7.5-fold higher in patients with a PSA doubling time < 12 months than in patients with a PSA doubling time > 12 months. The time to PSA relapse following a response to immediate ADT correlated significantly with baseline PSA, suggesting that baseline PSA may also reflect disease aggressiveness.

However, when early and delayed treatments were compared in a large randomised trial carried out by the Medical Research Council (MRC), a survival benefit for immediate hormone therapy was demonstrated (62), comparable with the results of the Lundgren et al. study mentioned above (22) (LE: 1b). In addition, a comparison of bicalutamide, 150 mg/day, with placebo showed that progression-free survival (PFS) was better with early treatment in patients with locally advanced PCa (23) (LE: 1b).
Fifty selected asymptomatic patients (mean age 71 years) with highly or moderately differentiated stage T3 M0 PCa were followed up for 169 months (53). The 5- and 10-year cancer-specific survival rates were 90% and 74%, respectively, and the likelihood of being without treatment at 5 and 10 years was 40% and 30%, respectively. The authors concluded that WW might be a treatment option for selected patients with non-poorly differentiated T3 tumours and a life expectancy of less than 10 years (LE: 3).

8.4 Deferred treatment for metastatic PCa (stage M1)

There are only very sparse data on this subject. The only candidates for such treatment should be asymptomatic patients with a strong wish to avoid treatment-related side-effects (LE: 4). As the median survival time is about 2 years, the time without any treatment (before symptoms occur) is very short in most cases. The MRC trial highlighted the risk of developing symptoms (pathological fractures, spinal cord compression), and even death from PCa, without receiving the possible benefit from hormone treatment (52,54) (LE:1b). If a deferred treatment policy is chosen for a patient with advanced PCa, close follow-up must be possible.

8.5 Summary of deferred treatment for prostate cancer

8.5.1 ***Indications***	**LE**
In presumed localised PCa (Nx-N0, M0):	
Stage T1a: well and moderately differentiated tumours. In younger patients with a life expectancy of more than 10 years, re-evaluation with PSA, TRUS and biopsies of the prostatic remnant is recommended.	2a
Stage T1b-T2b: well and moderately differentiated tumours. In asymptomatic patients with a life expectancy of < 10 years.	2a
Active surveillance	
In patients with the lowest risk of cancer progression: cT1-2a, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6 (at least 10 cores), ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	2a
Active surveillance selection is based on confirmatory biopsies.	
Follow-up is based on DRE, PSA and repeated biopsies. The optimal timing for follow-up is still unclear (yearly or every 2 years).	
The trigger for patients being moved off active treatment is based mainly on grade progression on repeated biopsies or at the patient's request.	
PSA progression is controversial.	
8.5.2 ***Options***	
In presumed localised PCa (Nx-N0, M0):	
Stage T1b-T2b patients who are well informed and have well-differentiated PCa and a life expectancy of 10-15 years.	
All patients not willing to accept side-effects of active treatment.	
Well-informed, asymptomatic patients with high PSA levels for whom cure is unlikely.	3
In locally advanced disease (stage T3-T4):	
Asymptomatic patients with well or moderately differentiated cancer, PCa and a short life expectancy.	3
PSA < 50 ng/mL and PSA doubling time > 12 months.	1
In metastatic disease (M1):	
A very rare patient without any symptoms and the possibility of close follow-up.	4

8.6 References

1. Cancer: fact and figures 2011. America cancer society. 2011 (web base: http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2011)
2. Haas GP, Delongchamps N, Brawley OW, et al. The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. Can J Urol 2008 Feb;15(1):3866-71. http://www.ncbi.nlm.nih.gov/pubmed/18304396
3. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin 2006;56(2):106-30. http://www.ncbi.nlm.nih.gov/pubmed/16514137
4. Adolfsson J. Watchful waiting and active surveillance: the current position. BJU Int 2008 Jul;102(1): 10-4. http://www.ncbi.nlm.nih.gov/pubmed/18422774
5. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. N Engl J Med 1994 Jan;330(4):242-8. http://www.ncbi.nlm.nih.gov/pubmed/8272085
6. Middleton RG, Thompson IM, Austenfeld MS, et al. Prostate Cancer Clinical Guidelines Panel Summary report on the management of clinically localized prostate cancer. The American Urological Association. J Urol 1995 Dec;154(6):2144-8. http://www.ncbi.nlm.nih.gov/pubmed/7500479
7. Thompson IM. Observation alone in the management of localized prostate cancer: the natural history of untreated disease. Urology 1994 Feb;43(2 Suppl):41-6. http://www.ncbi.nlm.nih.gov/pubmed/8116132
8. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998 Sep;280(11):969-74. http://www.ncbi.nlm.nih.gov/pubmed/9749478

9. Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. JAMA 2009 Sep 16;302(11):1202-9.
http://www.ncbi.nlm.nih.gov/pubmed/19755699
10. Sandblom G, Dufmats M, Varenhorst E. Long-term survival in a Swedish population-based cohort of men with prostate cancer. Urology 2000 Sep;56(3):442-7.
http://www.ncbi.nlm.nih.gov/pubmed/10962312
11. Johansson JE, Adami HO, Andersson SO, et al. Natural history of localized prostatic cancer. A population-based study in 223 untreated patients. Lancet 1989 Apr;1(8642):799-803.
http://www.ncbi.nlm.nih.gov/pubmed/2564901
12. Bill-Axelson A, Holmberg L, Ruutu M, et al. for the Scandinavian Prostate Cancer Group Study No. 4. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005 May;352(19):1977-84.
http://www.ncbi.nlm.nih.gov/pubmed/15888698
13. Adolfsson J, Tribukait B, Levitt S. The 20-yr outcome in patients with well- or moderately differentiated clinically localized prostate cancer diagnosed in the pre-PSA era: the prognostic value of tumour ploidy and comorbidity. Eur Urol 2007 Oct;52(4):1028-35.
http://www.ncbi.nlm.nih.gov/pubmed/17467883
14. Jonsson E, Sigbjarnarson HP, Tomasson J, et al. Adenocarcinoma of the prostate in Iceland: a population-based study of stage, Gleason grade, treatment and long-term survival in males diagnosed between 1983 and 1987. Scand J Urol Nephrol 2006;40(4):265-71.
http://www.ncbi.nlm.nih.gov/pubmed/16916765
15. Lowe BA. Management of stage T1a Prostate cancer. Semin Urol Oncol 1996 Aug;14(3):178-82.
http://www.ncbi.nlm.nih.gov/pubmed/8865481
16. Loughlin KR, Renshaw AA, Kumar S. Expectant management of stage A-1 (T1a) prostate cancer utilizing serum PSA levels: a preliminary report. J Surg Oncol 1999 Jan;70(1):49-53.
http://www.ncbi.nlm.nih.gov/pubmed/9989421
17. Albertsen PC, Hanley JA, Gleason DF, et al. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 1998 Sep;280(11):975-80.
http://www.ncbi.nlm.nih.gov/pubmed/9749479
18. Albertsen P, Hanley JA, Murphy-Setzko M. Statistical considerations when assessing outcomes following treatment for prostate cancer. J Urol 1999 Aug;162(2):439-44.
http://www.ncbi.nlm.nih.gov/pubmed/10411053
19. Iversen P, Johansson JE, Lodding P, et al. Scandinavian Prostatic Cancer Group. Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group Study Number 6. J Urol 2004 Nov;172(5Pt1):1871-6.
http://www.ncbi.nlm.nih.gov/pubmed/15540741
20. Bill-Axelson A, Holmberg L, Ruutu M, et al. SPCG-4 Investigators. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2011 May 5;364(18):1708-17.
http://www.ncbi.nlm.nih.gov/pubmed/21542742
21. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012 Jul 19;367(3):203-13.
http://www.ncbi.nlm.nih.gov/pubmed/22808955
22. Lundgren R, Nordle O, Josefsson K. Immediate estrogen or estramustine phosphate therapy Versus deferred endocrine treatment in nonmetastatic prostate cancer: a randomized multicenter study with 15 years of followup. The South Sweden Prostate Cancer Study Group. J Urol 1995 May;153(5): 1580-6.
http://www.ncbi.nlm.nih.gov/pubmed/7714978
23. Wirth MP, See WA, McLeod DG, et al. Casodex Early Prostate Cancer Trialists' Group. Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median followup of 5.4 years. J Urol 2004 Nov;172(5Pt1):1865-70.
http://www.ncbi.nlm.nih.gov/pubmed/15540740
24. Klotz L. Active surveillance for prostate cancer: trials and tribulations. World J Urol 2008 Sep;26(5):437-42.
http://www.ncbi.nlm.nih.gov/pubmed/18813934
25. Albertsen PC, Hanley JA, Barrows GH, et al. Prostate cancer and the Will Rogers phenomenon. J Natl Cancer Inst 2005 Sep;97(17):1248-53.
http://www.ncbi.nlm.nih.gov/pubmed/16145045

26. Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for prostate cancer. J Natl Cancer Inst 2003 Jun;95(12):868-78.
http://www.ncbi.nlm.nih.gov/pubmed/12813170
27. Törnblom M, Eriksson H, Franzén S, et al. Lead time associated with screening for prostate cancer. Int J Cancer 2004 Jan;108(1):122-9.
http://www.ncbi.nlm.nih.gov/pubmed/14618626
28. Klotz L. Active surveillance for favorable-risk prostate cancer: who, how and why? Nat Clin Pract Oncol 2007;4(12):692-8.
http://www.ncbi.nlm.nih.gov/pubmed/18037873
29. Albertsen PC, Moore DF, Shih W, et al. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol 2011 Apr 1;29(10):1335-41.
http://www.ncbi.nlm.nih.gov/pubmed/21357791
30. Droz JP, Balducci L, Bolla M, et al. Background for the proposal of SIOG guidelines for the management of prostate cancer in senior adults. Crit Rev Oncol Hematol 2010 Jan;73(1):68-91.
http://www.ncbi.nlm.nih.gov/pubmed/19836968
31. Johansson JE, Andrén O, Andersson SO, et al. Natural history of early, localized prostate cancer. JAMA 2004 Jun;291(22):2713-19.
http://www.ncbi.nlm.nih.gov/pubmed/15187052
32. Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol 2002 Apr;167(4):1664-9.
http://www.ncbi.nlm.nih.gov/pubmed/11912384
33. Choo R, DeBoer G, Klotz L, et al. PSA doubling time of prostate carcinoma managed with watchful observation alone. Int J Radiat Oncol Biol Phys 2001 Jul;50(3):615-20.
http://www.ncbi.nlm.nih.gov/pubmed/11395227
34. Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 2010 Jan 1;28(1):126-31.
http://www.ncbi.nlm.nih.gov/pubmed/19917860
35. Dall'Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. Cancer 2008 Jun 15;112(12):2664-70.
http://www.ncbi.nlm.nih.gov/pubmed/18433013
36. van den Bergh RC, Roemeling S, Roobol MJ, et al. Outcomes of men with screen-detected prostate cancer eligible for active surveillance who were managed expectantly. Eur Urol 2009 Jan;55(1):1-8.
http://www.ncbi.nlm.nih.gov/pubmed/18805628
37. van As NJ, Norman AR, Thomas K, et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. Eur Urol 2008 Dec;54(6):1297-305.
http://www.ncbi.nlm.nih.gov/pubmed/18342430
38. Soloway MS, Soloway CT, Eldefrawy A, Acosta K, Kava B, Manoharan M. Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. Eur Urol 2010 Dec;58(6):831-5.
39. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol 2011 Jun 1;29(16):2185-90.
http://www.ncbi.nlm.nih.gov/pubmed/21464416
40. Adamy A, Yee DS, Matsushita K, et al. Role of prostate specific antigen and immediate confirmatory biopsy in predicting progression during active surveillance for low risk prostate cancer. J Urol 2011 Feb;185(2):477-82.
http://www.ncbi.nlm.nih.gov/pubmed/21167529
41. Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. J Clin Oncol 2011 Sep 20;29(27):3669-76.
http://www.ncbi.nlm.nih.gov/pubmed/21825257
42. Lawrentschuk N, Haider MA, Daljeet N, et al. 'Prostatic evasive anterior tumours': the role of magnetic resonance imaging. BJU Int 2010 May;105(9):1231-6.
http://www.ncbi.nlm.nih.gov/pubmed/19817743
43. Ploussard G, Durand X, Xylinas E, et al. Prostate cancer antigen 3 score accurately predicts tumour volume and might help in selecting prostate cancer patients for active surveillance. Eur Urol 2011 Mar;59(3):422-9.
http://www.ncbi.nlm.nih.gov/pubmed/21156337

44. Berglund RK, Masterson TA, Vora KC, et al. Pathological upgrading and up staging with immediate repeat biopsy in patients eligible for AS. J Urol 2008 Nov;180(5):1964-7; discussion 1967-8. http://www.ncbi.nlm.nih.gov/pubmed/18801515
45. Al Otaibi M, Ross P, Fahmy N, et al. Role of repeated biopsy of the prostate in predicting disease progression in patients with prostate cancer on active surveillance. Cancer 2008 Jul 15;113(2):286-92. http://www.ncbi.nlm.nih.gov/pubmed/18484590
46. Ross AE, Loeb S, Landis P, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. J Clin Oncol 2010 Jun;28(17): 2810-6. http://www.ncbi.nlm.nih.gov/pubmed/20439642
47. Steineck G, Helgesen F, Adolfsson J, et al. Scandinavian Prostatic Cancer Group Study Number 4. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002 Sep 12;347(11): 790-6. http://www.ncbi.nlm.nih.gov/pubmed/12226149
48. Rana A, Chisholm GD, Khan M, et al. Conservative management with symptomatic treatment and delayed hormonal manipulation is justified in men with locally advanced carcinoma of the prostate. Br J Urol 1994 Nov;74(5):637-41. http://www.ncbi.nlm.nih.gov/pubmed/7827816
49. Parker MC, Cook A, Riddle PR, et al. Is delayed treatment justified in carcinoma of the prostate? Br JUrol 1985 Dec;57(6):724-8. http://www.ncbi.nlm.nih.gov/pubmed/4084734
50. Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006 Apr;24(12):1868-76. http://www.ncbi.nlm.nih.gov/pubmed/16622261
51. Studer UE, Collette L, Whelan P, et al. EORTC Genitourinary Group. Using PSA to guide timing of androgen deprivation in patients with T0-4 N0-2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). Eur Urol 2008 May;53(5):941-9. http://www.ncbi.nlm.nih.gov/pubmed/18191322
52. [No authors listed] The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. Br J Urol 1997 Feb;79(2):235-46. http://www.ncbi.nlm.nih.gov/pubmed/9052476
53. Adolfsson J, Steineck G, Hedlund PO. Deferred treatment of locally advanced non-metastatic prostate cancer: a long-term followup. J Urol 1999 Feb;161(2):505-8. http://www.ncbi.nlm.nih.gov/pubmed/9915436
54. Walsh PC. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. J Urol 1997 Oct;158(4):1623-4. http://www.ncbi.nlm.nih.gov/pubmed/9302187

9. TREATMENT: RADICAL PROSTATECTOMY

9.1 Introduction

The surgical treatment of prostate cancer (PCa) consists of radical prostatectomy (RP), which involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by bilateral pelvic lymph node dissection. In men with localised PCa and a life expectancy ≥ 10 years, the goal of RP by any approach must be eradication of disease, while preserving continence and whenever possible potency (1). There is no age threshold for RP and a patient should not be denied this procedure on the grounds of age alone (2). Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes (3). An estimation of life expectancy is paramount in counselling a patient about surgery (4).

Currently, RP is the only treatment for localised PCa to show a benefit for OS and cancer-specific survival (CSS), compared with conservative management, as shown in one prospective randomised trial (5). After a follow-up of 15 years, the SPCG-4 trial showed that RP was associated with a reduction of all-cause mortality: RR=0.75 (0.61 to 0.92). According to a post hoc statistical sub-group analysis, the number to treat (NNT) to avert one death was 15 overall and 7 for men younger than 65 years of age. Radical prostatectomy

was also associated with a reduction in prostate cancer-specific mortality: RR=0.62 (0.44 to 0.87). This OS and CSS benefit could not be reproduced for the overall study population in another prospective randomised trial. After a median follow-up of 10 years, the PIVOT trial showed that RP did not significantly reduce all-cause mortality: HR=0.88 (0.71 to 1.08); p=0.22, nor did RP significantly reduce prostate cancer mortality: HR=0.63 (0.36 to 1.09); p=0.09. According to a preplanned sub-group analysis among men with low-risk tumours (n=296), RP non-significantly increased all-cause mortality: HR=1.15 (0.80 to 1.66). Among men with intermediate-risk tumours (n=249), RP significantly reduced all-cause mortality: HR=0.69 (0.49 to 0.98). Among men with high-risk tumours (n=157), RP non-significantly reduced all-cause mortality: HR=0.40 (0.16 to 1.00). Among men with PSA > 10, RP significantly reduced all cause mortality: HR=0.67 (0.48 to 0.94).

Surgical expertise has decreased the complication rates of RP and improved cancer cure (6-10). If performed by an experienced surgeon, the patient's subsequent quality of life should be satisfactory. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, adjusted for the characteristics of the cancer being treated, can decrease positive surgical margin rates and improve cancer control with RP (11,12).

Radical retropubic prostatectomy (RRP) and perineal prostatectomy are performed through open incisions, and more recently, minimally invasive laparoscopic radical prostatectomy (LRP) and robot-assisted laparoscopic prostatectomy (RALP) have been developed. RALP is displacing RRP as the gold standard surgical approach for clinically localised PCa in the United States and is also being increasingly used in Europe and other parts of the world. This trend has occurred despite the paucity of high-quality evidence to support its superiority over more-established treatment modalities. Recent in-depth systematic reviews of the literature have compared the results of RRP versus LRP/RALP.

Robot-assisted laparoscopic prostatectomy is associated with less blood loss and transfusion rates comparable to RRP, and there appear to be minimal differences between the two surgical approaches in terms of overall post-operative complications. Positive surgical margin rates are at least equivalent to RARP, but firm conclusions about biochemical recurrence and other oncologic end-points are difficult to draw due to the relatively short follow-up in the published literature and the fact that the overall experience with RARP in locally advanced PCa is still limited. RARP may offer advantages in postoperative recovery for urinary continence and erectile function, although most published studies addressing these outcomes suffer from methodological limitations. There is a need for well-controlled comparative outcomes studies of RP surgery following best practice guidelines.(13-17).

9.2 Low-risk, localised prostate cancer: cT1-T2a and Gleason score 2-6 and prostate-specific antigen < 10 ng/mL

Patients with low-risk, localised PCa should be informed about the results of two randomised trials comparing retropubic RP versus watchful waiting (WW) in localised PCa. In the SPCG-4 study, the survival benefit was similar before and after 9 years of follow-up and was also observed in men with low-risk PCa, and was confined to men < 65 years of age. In the PIVOT-trail, a preplanned sub-group analysis of men with low-risk tumours, showed that RP did not significantly reduce all-cause mortality.

*9.2.1 **Stage T1a-T1b prostate cancer***

Stage T1a PCa is defined as an incidental histological finding of cancer in ≤ 5% of resected prostatic tissue [transurethral resection of the prostate (TURP) or open adenomectomy]. Stage T1b PCa is defined as > 5% cancer. Published series have shown a pT0 stage in 4-21% and an organ-confined stage in 47-85% of patients at subsequent RP (18).

A Swedish register-based study of 23,288 men with incidental PCa detected at TURP or open adenoma enucleation, mostly before the prostate-specific antigen (PSA) era, showed a 10-year PCa mortality of 26.6%. There were no details of the PSA level or Gleason score, nor the numbers of cases with cT1a or cT1b PCa (19). Other older studies have shown that, even though the risk of disease progression of untreated T1a PCa after 5 years is only 5%, these cancers can progress in about 50% of cases after 10-13 years (20). Thus, it was believed that, in younger patients with a life-expectancy of ≥ 15 years, the chance of disease progression was real. In contrast, most patients with T1b tumours were expected to show disease progression after 5 years, and aggressive treatment was often warranted (20). Patients with T1b lesions were offered RP when they had a life expectancy of ≥ 10 years.

Nevertheless, it remains unclear whether these findings would still be valid in the PSA era. In a recent analysis of T1a/b PCa:

- The only significant predictors of the presence of residual cancer at RRP were PSA measured before and after surgery for benign prostatic hyperplasia (BPH) and Gleason score at surgery for BPH.
- The only independent predictors of biochemical recurrence after RRP were PSA measured after

surgery for BPH and Gleason score at surgery for BPH.
- The stage (cT1a or cT1b) lost its significance in predicting the above-mentioned outcomes.

A predictive model has been proposed, which incorporates the PSA level before and after surgery and the Gleason score at surgery for BPH. The model has a predictive accuracy of 83.2% for estimating residual tumour and 87.5% for estimating biochemical progression, but needs external validation before it can be used in daily practice (18).

Systematic prostate biopsies of the remnant prostate may be useful in detecting residual cancer or concomitant peripheral zone cancer, or to ascertain a more correct tumour grade. Radical prostatectomy may be difficult after thorough TURP, when almost no residual prostate is left behind (21).

9.2.2 ***Stage T1c and T2a prostate cancer***

Clinically unapparent tumour identified by needle biopsy because of an elevated PSA (cT1c) has become the most prevalent type of PCa. In an individual patient, it is difficult to differentiate between clinically insignificant and life-threatening PCa. Most reports, however, stress that cT1c tumours are mostly significant and should not be left untreated because up to 30% of cT1c tumours are locally advanced at final histopathological analysis (22). The proportion of insignificant tumours varies between 11% and 16% (23,24). Increasing the number of biopsies may carry the risk of detecting a higher number of insignificant cancers. However, a recent study has shown that increasing the number of biopsies to 12 did not increase the number of insignificant tumours (25). The major problem is how to recognise those tumours that do not need RP. The biopsy findings and the free PSA ratio are helpful in predicting insignificant disease (26). Partin tables may help better selection of patients who require surgical treatment, because of their ability to provide an estimation of the final pathological stage (27). Other authors have suggested the incorporation of biopsy information, such as the number of cores or the percentage of cores invaded (28). When only one or a few cores are invaded and the percentage of invasion in one core is limited, the chance of finding an insignificant PCa is more likely, certainly when the lesion is of low Gleason score (29). It might be reasonable to follow-up some patients whose tumours are most likely to be insignificant.

In general, however, RP should be advocated for patients with T1c tumours, bearing in mind that significant tumours will be found in most of these individuals. Stage T2a patients with a 10-year life expectancy should be offered RP because 35-55% of them will have disease progression after 5 years if not treated. If active monitoring is proposed for low-grade T2 cancer, it should be remembered that preoperative assessment of tumour grade by needle biopsy is often unreliable (30).

Extended pelvic lymph node dissection (eLND) is not necessary in low-risk, localised PCa, because the risk for positive lymph nodes does not exceed 5% (31).

9.3 Intermediate-risk, localised prostate cancer: cT2b-T2c or Gleason score = 7 or prostate-specific antigen 10-20 ng/mL

Patients with intermediate-risk, localised PCa should be informed about the results of two randomised trials comparing RRP vs. WW in localised PCa. In the SPCG-4 study, the survival benefit was similar before and after 9 years of follow-up and was confined to men < 65 years of age. The number needed to treat to avert one death was 15 overall and seven for men < 65 years of age. In the PIVOT-trial, a preplanned sub-group analysis of men with intermediate-risk tumours, RP did significantly reduce all-cause mortality.

Radical prostatectomy is one of the recommended standard treatments for patients with intermediate-risk PCa and a life expectancy of > 10 years (32). The prognosis is excellent when the tumour is confined to the prostate, based on pathological examination (33,34). A policy of WW has been proposed for some patients with intermediate-risk localised tumours (35). However, when the tumour is palpable or visible on imaging and clinically confined to the prostate, disease progression can be expected in most long-term survivors.
The median time to progression of untreated T2 disease has been reported as 6-10 years. Stage T2b cancer confined to the prostate, but involving more than half a lobe or both lobes, will progress in > 70% of patients within 5 years (36). These data have been confirmed by a large RCT which included mostly T2 PCa patients and compared RP and WW. The results showed a significant reduction in disease-specific mortality in favour of RP (5). Another large RCT corroborated these results (6).

An eLND should be performed in intermediate-risk, localised PCa if the estimated risk for positive lymph nodes exceeds 5% (31). In all other cases, eLND can be omitted, which means accepting a low risk of missing positive nodes. Limited LND should no longer be performed, because this misses at least half of the nodes involved.

9.3.1 ***Oncological results of radical prostatectomy in low- and intermediate-risk prostate cancer***

The results achieved in a number of studies involving RP are shown in Table 14.

Table 14: Oncological results of RP in organ-confined disease

Reference	No. of patients	Year of RP	Median follow-up (mo)	10-year PSA-free survival (%)	10-year cancer-specific survival (%)	15-year cancer-specific survival (%)	25-year cancer-specific survival (%)
Isbarn *et al*. (2009) (37)	436	1992-97	122	60	94		
Roehl *et al*. (2004) (38)	3478	1983-2003	65	68	97		
Han *et al*. (2001) (39)	2404	1982-99	75	74	96	90	
Hull *et al*. (2002) (40)	1000	1983-98	53	75	98		
Porter *et al*. (2006) (41)	752	1954-94	137	71	96	91	82
Bill-Axelson *et al*. (2011) (5)	347	1989-99	153			85	
Stephenson et al. (42)	6398	1987-2005	48			88	

The first externally validated nomogram predicting PCa-specific mortality after RP for patients treated in the PSA era was published in 2009. The nomogram predicts that few patients die from PCa within 15 years of RP, despite the presence of adverse clinical features. This nomogram can be used in patient counselling and clinical trial design (42).

9.4 High-risk localised and locally advanced prostate cancer: cT3a or Gleason score 8-10 or prostate-specificantigen > 20 ng/mL

The widespread use of PSA testing has led to a significant migration in stage and grade of PCa, with > 90% of men in the current era diagnosed with clinically localised disease (27). Despite the trends towards lower-risk PCa, 20-35% of patients with newly diagnosed PCa are still classified as high risk, based on either PSA > 20 ng/mL, Gleason score > 8, or an advanced clinical stage (43). Patients classified with high-risk PCa are at an increased risk of PSA failure, the need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor prognosis after RP (44).

There is no consensus regarding the optimal treatment of men with high-risk PCa. Decisions on whether to elect surgery as local therapy should be based on the best available clinical evidence. Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with a low tumour volume. Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances.

9.4.1 ***Locally advanced prostate cancer: cT3a***

Stage T3a cancer is defined as cancer that has perforated the prostate capsule. In the past, locally advanced PCa was seen in about 40% of all clinically diagnosed tumours. This figure is lower today, although its management remains controversial. Surgical treatment of clinical stage T3 PCa has traditionally been discouraged (45), mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse (46,47). Several randomised studies of radiotherapy combined with ADT versus radiotherapy alone have shown a clear advantage for combination treatment, but no trial has ever proven combined treatment to be superior to RP (48). Another problem is “contamination” by the additional use of either adjuvant radiotherapy or immediate or delayed hormonal therapy (HT) in most series reporting the treatment of clinical T3 PCa. In recent years, there has been renewed interest in surgery for locally advanced PCa, and several retrospective case series have been published. Although still controversial, it is increasingly evident that surgery has a place in treating locally advanced disease (49-51).

Over-staging of cT3 PCa is relatively frequent and occurs in 13-27% of cases. Patients with pT2 disease and those with specimen-confined pT3 disease have similarly good biochemical and clinical PFS (50,51). In 33.5-66% of patients, positive section margins are present, and 7.9-49% have positive lymph nodes (52). Thus, 56-78% of patients primarily treated by surgery eventually require adjuvant or salvage radiotherapy or HT (50,51). Nevertheless, excellent 5-, 10- and 15-year OS and CSS rates have been published (Table 15). These rates surpass radiotherapy-alone and are no different from radiotherapy combined with adjuvant HT (48).

The problem remains the selection of patients before surgery. Nomograms, including PSA level, stage and Gleason score, can be useful in predicting the pathological stage of disease (27,52). In addition, nodal imaging with CT, and seminal vesicle imaging with MRI, or directed specific puncture biopsies of the nodes or seminal vesicles can help to identify those patients unlikely to benefit from a surgical approach (53). Radical prostatectomy for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable. Increased overall surgical experience must contribute to decreased operative morbidity and to better functional results after RP for clinical T3 cancer (50,54). It has been shown that continence can be preserved in most cases, and in selected cases, potency can also be preserved (55).

Table 15: OS and CSS rates for locally advanced PCa.

Reference	no. of patients	Median and/ or mean follow-up	BPFS (%)			CSS (%)		
			5 years	10 years	15 years	5 years	10 years	15 years
Gerber *et al*. (1997) (49)	242	Mean, 39 months Median, 26 months	-	-	-	85	57	-
Ward *et al*. (2005) (53)	841	Median, 10.3 years	58 (PSA > 0.4)	43	38	95	90	79
Hsu *et al*. (2007) (54)	200	Mean, 70.6 months (cT3a only)	59.5 (PSA > 0.2)	51.1	-	99	92	-

BPFS = biochemical progression-free survival

*9.4.2 **High-grade prostate cancer: Gleason score 8-10***

Although most poorly differentiated tumours extend outside the prostate, the incidence of organ-confined disease is 26-31%. Patients with high-grade tumours confined to the prostate at histopathological examination still have a good prognosis after RP. Furthermore, one-third of patients with a biopsy Gleason score ≥ 8 may in fact have a specimen Gleason score ≤ 7 with better prognostic characteristics. The PSA value and percentage of positive prostate biopsies may help to select men with high-grade PCa who are most likely to benefit from RP (56).

*9.4.3 **Prostate cancer with prostate-specific antigen > 20 ng/mL***

Yossepowitch et al. have reported the results of RP as monotherapy in men with PSA > 20 ng/mL, in a cohort with mostly clinically organ-confined tumours, and found a PSA failure rate of 44% and 53% at 5 and 10 years, respectively (44). D'Amico et al. found that men with PSA levels > 20 ng/mL had a 50% risk of PSA failure at 5 years after RP (57). Spahn et al. published the largest multicentre surgical series to date, including 712 patients with PSA > 20 ng/mL, and reported a CSS of 90% and 85% at 10 and 15 years follow-up, respectively (58). In the same analysis, they demonstrated that the combination of PSA > 20 ng/mL with cT3 stage and/or biopsy Gleason score 8-10 significantly lowered CSS. More recently, Gontero and co-workers described a subanalysis of the same patient cohort. Ten-year CSS was 80%, 85% and 91% in patients with PSA > 100 ng/mL, 50.1-100 ng/mL and 20.1-50 ng/mL, respectively. These results argue for aggressive management with RP as the initial step (59).

Extended LND should be performed in all high-risk cases, because the estimated risk for positive lymph nodes is 15-40% (31). Limited LND should no longer be performed, because it misses at least half the nodes involved.

9.5 Very-high-risk, localised prostate cancer: cT3b-T4 N0 or any T, N1

*9.5.1 **cT3b-T4 N0***

Men with very-high-risk PCa generally have a significant risk of disease progression and cancer-related death

if left untreated. Very-high-risk PCa presents two specific challenges. There is a need for local control as well as treatment of any microscopic metastases that are likely to be present but undetectable until disease progression.
The optimal treatment approach therefore often necessitates multiple modalities. The exact combinations, timing and intensity of treatment continue to be strongly debated. A recent US study has shown that 72 patients who underwent RP for cT4 disease had better survival than those who received HT or radiotherapy alone, and comparable survival to men who received radiotherapy plus HT (60). Another study has compared the outcomes of RP in very-high-risk PCa (T3-T4 N0-N1, N1, M1a) with those in localised PCa. The two groups did not differ significantly in surgical morbidity except for blood transfusion, operative time, and lymphoceles, which showed a higher rate in patients with advanced disease. Overall survival and CSS at 7 years were 76.69% and 90.2% in the advanced disease group and 88.4% and 99.3% in the organ-confined disease group, respectively (61).

Provided that the tumour is not fixed to the pelvic wall, or there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with very-high-risk PCa and low tumour volume. Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances.

*9.5.2 **Any T, N1***

The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement. Clinical lymph node-positive (N+) disease will mostly be followed by systemic disease progression, and all patients with significant N+ disease ultimately fail treatment.

Nevertheless, the combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% (62,63). Most urologists are reluctant to perform RP for clinical N+ disease, or cancel surgery if a frozen section shows lymph node invasion. However, a retrospective observational study has shown a dramatic improvement in CSS and OS in favour of completed RP vs. abandoned RP in patients who were found to be N+ at the time of surgery. These results suggest that RP may have a survival benefit and the abandonment of RP in N+ cases may not be justified (64). These findings have been corroborated in a contemporary retrospective analysis (65). Radical prostatectomy resulted in superior survival of patients with N+ PCa after controlling for lymph node tumour burden. The findings from these studies support the role of RP as an important component of multimodal strategies of N+ PCa.

The incidence of tumour progression is lower in patients with fewer positive lymph nodes and in those with microscopic invasion only (66,67). In patients who prove to be pN+ after RP, early adjuvant HT has been shown to improve CSS and OS significantly in a prospective randomised trial. However, this trial included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics. It is unclear whether early adjuvant HT should still be used in the present era of increased detection of microscopic involvement as a result of more eLND. The benefits should be judged against the side effects of long-term HT. Follow-up of PSA and delayed start of HT in patients with rising PSA level is therefore an acceptable option in selected cases. Interestingly, maximal local control with radiotherapy of the prostatic fossa appears to be beneficial in PCa patients with pN+ after RP, treated adjuvantly with continuous ADT (68).

9.6 Indication and extent of extended pelvic lymph node dissection

Although it is generally accepted that eLND provides important information for prognosis (number of nodes involved, tumour volume within the lymph node, and capsular perforation of the node) that cannot be matched by any other current procedure, consensus has not been reached about when eLND is indicated and to what extent it should be performed. When making such decisions, many physicians rely on nomograms based on preoperative biochemical markers and biopsies (27).

According to these nomograms, patients with PSA < 10 ng/mL and biopsy Gleason score < 7 have a low risk of lymph node metastasis, and therefore, eLND might not be beneficial. However, the fact that most nomograms are based on a limited eLND (obturator fossa and external iliac vein) probably results in underestimation of the incidence of patients with positive nodes (31). Lymphography studies have shown that the prostate drains not only to the obturator and external iliac lymph nodes but also to the internal iliac and presacral nodes. Performing eLND results in removal of all lymph nodes in these particular anatomical regions, producing a higher yield of excised lymph nodes (mean: 20 nodes) compared with limited LND (mean: 8-10 nodes).

In patients with PSA < 10 ng/mL and Gleason score ≥ 7, the incidence of nodal involvement has been reported as 25% (69). Different reports mention that 19-35% of positive lymph nodes are found exclusively outside the area of the traditionally limited LND (70,71). Clearly, the removal of a greater number of nodes results in improved staging. In the largest study of its kind, a cut-off ≤ 2 vs. > 2 affected nodes was shown to

be an independent predictor of CSS (66).

*9.6.1 **Extent of extended lymph node dissection***

Extended LND includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal ileac artery. Some lymph node mapping studies have advocated extending the template to include the common iliac lymph nodes up to the ureteric crossing. With this template, 75% of all anatomical landing sites are cleared (72). For eLND to be representative, a mean of 20 lymph nodes should be removed (73). It is recommended that the nodes should be sent in separate containers for each region for histopathological analysis, because this will usually be associated with a higher diagnostic gain by the uropathologist.

*9.6.2 **Therapeutic role of extended lymph node dissection***

Besides being a staging procedure, pelvic LND/eLND can be curative, or at least beneficial, in a subset of patients with limited lymph node metastases (74-76). In some series, the number of nodes removed during lymphadenectomy has correlated significantly with time to progression (77). In one population-based study with a 10-year follow-up, patients undergoing excision of at least four lymph nodes (node-positive and node-negative patients) or > 10 nodes (only node-negative patients) had a lower risk of PCa-specific death at 10 years than those who did not undergo lymphadenectomy (78). Further studies should confirm these results.

*9.6.3 **Morbidity***

Pelvic eLND remains a surgical procedure that increases morbidity in the treatment of PCa. When comparing extended vs. limited LND, threefold higher complication rates have been reported by some authors (79). Complications consist of lymphocoeles, lymphoedema, deep venous thrombosis, and pulmonary embolism. Other authors, however, have reported more acceptable complication rates (80,81).

*9.6.4 **Conclusions extended lymph node dissection***

Extended LND may play a role in the treatment of a subset of intermediate-risk cases with > 5% nomogram predicted risk of positive lymph nodes, and in all high-risk cases.
Extended LND may increase staging accuracy and influence decision making with respect to adjuvant therapy. The number of lymph nodes removed correlates with time to progression.
Surgical morbidity must be balanced against the therapeutic effects, and decisions need to be made based on an individual cases.

9.7 Summary of radical prostatectomy and eLND in high-risk localised disease

RP is a reasonable treatment option in selected patients with cT3a PCa, Gleason score 8-10 or PSA > 20. Furthermore, RP is optional in highly selected patients with cT3b-4 N0 or any cT N1 PCa in the context of a multimodality approach.
Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances.
If RP is performed, pelvic eLND must be performed, because lymph node involvement is common.
The patient must be informed about the likelihood of a multimodal approach. In case of adverse tumour characteristics (positive section margin, extraprostatic extension, or seminal vesicle invasion), adjuvant radiotherapy may reasonably be used after recuperation from surgery.
When nodal involvement is detected after surgery, adjuvant ADT may be selected.
Extended LND is not necessary in low-risk, localised PCa, because the risk for positive lymph nodes does not exceed 5%.
Extended LND should be performed in intermediate-risk, localised PCa if the estimated risk for positive lymph nodes exceeds 5%, as well as in high-risk cases. In these circumstances, the estimated risk for positive lymph nodes is 15-40%.
Limited LND should no longer be performed, because it misses at least half the nodes involved.

RP = radical prostatectomy; PCa = prostate cancer; eLND = extended lymph node dissection; ADT = androgen-deprivation therapy.

9.8 Neoadjuvant hormonal therapy and radical prostatectomy

Neoadjuvant or up-front HT is defined as therapy given before definitive local curative treatment (e.g., surgery or radiotherapy). PCa is an androgen-dependent tumour, therefore, neoadjuvant hormonal therapy (NHT) is an appealing concept. Attempts to decrease the size of the prostate before RP were first reported by Vallett as early as 1944 (82). In a recent review and meta-analysis, the role of NHT and prostatectomy has been studied (83). NHT before prostatectomy did not improve OS or disease-free survival (DFS), but did significantly reduce positive margin rates [relative risk (RR): 0.49; 95% confidence interval (CI): 0.42-0.56, P < 0.00001), organ confinement (RR: 1.63; 95% CI: 1.37-1.95, P < 0.0001) and lymph node invasion (RR: 0.49; 95% CI: 0.42-0.56, P < 0.02). Thus, the absence of improvement in clinically important outcomes (OS, disease-specific survival or biochemical DFS) was demonstrated despite improvements in putative pathological surrogate outcomes, such as margin-free positive status. This calls into question the use of these pathological markers of treatment outcomes as valid surrogates for clinically relevant outcomes.

Further studies are needed to investigate the application of HT as both neoadjuvant treatment and with chemotherapy in early disease. More information is also needed to evaluate these agents in terms of side effects and quality of life, which was lacking in most studies presented in this review.

Further cost analyses should be undertaken to update the data. A recent Cochrane review and meta-analysis have studied the role of adjuvant HT following RP: the pooled data for 5-year OS showed an odds ratio (OR) of 1.50 and 95% CI: 0.79-2.84. This finding was not statistically significant, although there was a trend favouring adjuvant HT. Similarly, there was no survival advantage at 10 years. The pooled data for DFS gave an overall OR of 3.73 and 95% CI: 2.3-6.03. The overall effect estimate was highly significant (P < 0.00001) in favour of the HT arm.

It is noteworthy that the Early Prostate Cancer Trialists' Group (EPC) trial was not included in the Cochrane review. The third update from this large randomised trial of bicalutamide, 150 mg once daily, in addition to standard care in localised and locally advanced, non-metastatic PCa was published in November 2005 (84). Median follow-up was 7.2 years. There was a significant improvement in objective PFS in the RP group. This improvement was only significant in the locally advanced disease group [hazard ratio (HR): 0.75; 95% CI: 0.61-0.91]. There was no significant improvement in OS in the RP-treated groups (localised and locally advanced disease). In the WW group, there was an OS trend in favour of WW alone in the localised disease group (HR: 1.16; 95% CI: 0.99-1.37).

*9.8.1 **Summary of neoadjuvant and adjuvant hormonal treatment and radical prostatectomy***

NHT before RP does not provide a significant OS advantage over prostatectomy alone.
NHT before RP does not provide a significant advantage in DFS over prostatectomy alone.
NHT before RP does substantially improve local pathological variables such as organ-confined rates, pathological down-staging, positive surgical margins, and rate of lymph node involvement.
Adjuvant HT following RP shows no survival advantage at 10 years.
Adjuvant HT following RP: the overall effect estimate for DFS is highly significantly (P < 0.00001) in favour of the HT arm.

9.9 Complications and functional outcome

The postoperative complications of RP are listed in Table 16. The mortality rate is 0-1.5% (81); urinary fistulae are seen in 1.2-4% of patients (85); and urinary incontinence persists after 1 year in 7.7% (86). In men undergoing prostatectomy, the rates of postoperative and late urinary complications are significantly reduced if the procedure is performed in a high-volume hospital and by a surgeon who performs a large number of such procedures (87-89).

Erectile dysfunction used to occur in nearly all patients, but this can be avoided by using nerve-sparing techniques in early-stage disease (90). Patients who benefit from nerve-sparing RP may have a higher chance of local disease recurrence and should therefore be selected carefully.

Table 16: Complications of RP

Complication	Incidence (%)
Perioperative death	0.0-2.1
Major bleeding	1.0-11.5
Rectal injury	0.0-5.4
Deep venous thrombosis	0.0-8.3
Pulmonary embolism	0.8-7.7
Lymphocoele	1.0-3.0
Urine leak, fistula	0.3-15.4
Slight stress incontinence	4.0-50.0
Severe stress incontinence	0.0-15.4
Impotence	29.0-100.0
Bladder neck obstruction	0.5-14.6
Ureteral obstruction	0.0-0.7
Urethral stricture	2.0-9.0

9.10 Summary of indications for nerve-sparing surgery* (100-104)

Reference name	Sofer (91)	Walsh (92)	Alsikafi (93)	Graefen (94)	Bianco (95)
Preoperative selection criteria					
Stage > T2	+	+	+	+	+
PSA > 10	+				
Biopsy Gleason score 7			+		
Biopsy Gleason score 8-10	+			+	
Partin tables		+			+
Side with > 50% tumour in biopsy			+		
Side with perineural invasion		+/-	+		
Intra-operative selection criteria					
Side of palpable tumour			+		
Side of positive biopsy				+	
Induration of lateral pelvic fascia		+			+
Adherence to neurovascular bundles		+			+
Positive section margins	**24%**	**5%**	**11%**	**15.9%**	**5%**

**Clinical criteria used by different authors when NOT to perform a nerve-sparing RP*

Nerve-sparing RP can be performed safely in most men undergoing RP (96,97). In the past decade, a dramatic shift towards lower-stage tumours has become evident. More importantly, men are younger at the time of diagnosis and more interested in preserving sexual function. Nevertheless, clear contraindications are patients in whom there is a high risk of extracapsular disease, such as any cT3 PCa, cT2c, any Gleason score > 7 on biopsy, or more than one biopsy > 6 at the ipsilateral side. Partin tables help to guide decision making (27).

If any doubt remains regarding residual tumour, the surgeon should remove the neurovascular bundle (NVB). Alternatively, the use of intraoperative frozen-section analysis can help guide these decisions. This is especially helpful in patients with a lesion palpable close to the capsule during nerve-sparing RP. A wedge of the prostate can then be resected and inked differently. In case carcinoma is adherent to the capsule on frozen section analysis, the NVB is resected; otherwise, the NVB remains in situ. In patients with intraoperatively detected tumour lesions during nerve-sparing, planned RP, frozen-section analysis objectively supports the decision of secondary NVB resection, as well as preservation (98).

The patient must be informed before surgery about the risks of nerve-sparing surgery, the potency rates achieved, and the possibility that, to ensure adequate cancer control, the nerves may be sacrificed despite any preoperative optimism favouring the potential for their salvage.

The early administration of intracavernous injection therapy could improve the definitive potency rates (99,100). Finally, the early use of phosphodiesterase-5 inhibitors in penile rehabilitation remains controversial. A placebo-controlled prospective study has shown no benefit from daily early administration of vardenafil vs. on-demand vardenafil in the postoperative period (101), whereas another placebo-controlled prospective study has shown that sildenafil has a significant impact on return of normal spontaneous erections (102).

9.11 Conclusions and recommendations for radical prostatectomy

Indications	**LE**
In patients with low and intermediate risk localised PCa (cT1a-T2b and Gleason score 2-7 and PSA ≤ 20 ng/mL) and life expectancy > 10 years.	1b
Optional	
Patients with stage T1a disease and a life expectancy >15 years or Gleason score 7.	3
Selected patients with low-volume, high-risk, localised PCa (cT3a or Gleason score 8-10 or PSA > 20 ng/mL).	3
Highly selected patients with very-high-risk, localised PCa (cT3b-T4 N0 or any T N1) in the context of multimodality treatment.	3
Short-term (3 months) or long-term (9 months) neoadjuvant therapy with gonadotrophin-releasing hormone analogues is NOT recommended for the treatment of stage T1-T2 disease.	1a
Nerve-sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c, Gleason score < 7 and PSA < 10 ng/mL or see Partin tables/nomograms).	3
Unilateral nerve-sparing procedures are an option in stage T2a-T3a disease.	4

9.12 References

1. Bianco FJ Jr, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology 2005 Nov;66(5 Suppl):83-94. http://www.ncbi.nlm.nih.gov/pubmed/16194712
2. Droz JP, Balducci L, Bolla M, et al. Background for the proposal of SIOG guidelines for the management of prostate cancer in senior adults. Crit Rev Oncol Hematol 2010 Jan;73(1):68-91. http://www.ncbi.nlm.nih.gov/pubmed/19836968
3. Albertsen PC, Moore DF, Shih W, et al. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol 2011 Apr;29(10):1335-41. http://www.ncbi.nlm.nih.gov/pubmed/21357791
4. Walz J, Gallina A, Saad F, et al. A nomogram predicting 10-year life expectancy in candidates for radical prostatectomy or radiotherapy for prostate cancer. J Clin Oncol 2007 Aug;25(24):3576-81. http://www.ncbi.nlm.nih.gov/pubmed/17704404
5. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2011 May;364(18):1708-17. http://www.ncbi.nlm.nih.gov/pubmed/21542742
6. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012 Jul 19;367(3):203-13. http://www.ncbi.nlm.nih.gov/pubmed/22808955
7. Potosky AL, Warren JL. Radical prostatectomy: does higher volume lead to better quality? J Natl Cancer Inst 1999 Nov;91(22):1906-7. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/10564667
8. Lepor H, Nieder AM, Ferrandino MN. Intraoperative and postoperative complications of radical retropubic prostatectomy in a consecutive series of 1,000 cases. J Urol 2001 Nov;166(5):1729-33. http://www.ncbi.nlm.nih.gov/pubmed/11586211
9. Augustin H, Hammerer P, Graefen M, et al. Intraoperative and perioperative morbidity of contemporary radical retropubic prostatectomy in a consecutive series of 1243 patients: results of a single center between 1999 and 2002. Eur Urol 2003 Feb;43(2):113-8. http://www.ncbi.nlm.nih.gov/pubmed/12565767
10. Maffezzini M, Seveso M, Taverna G, et al. Evaluation of complications and results in a contemporary series of 300 consecutive radical retropubic prostatectomies with the anatomic approach at a single institution. Urology 2003 May;61(5):982-6. http://www.ncbi.nlm.nih.gov/pubmed/12736020
11. Eastham JA, Kattan MW, Riedel E, et al. Variations among individual surgeons in the rate of positive surgical margins in radical prostatectomy specimens. J Urol 2003 Dec;170(6 Pt 1):2292-5. http://www.ncbi.nlm.nih.gov/pubmed/14634399

12. Vickers AJ, Savage CJ, Hruza M, et al. The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study. Lancet Oncol 2009 May;10(5):475-80. http://www.ncbi.nlm.nih.gov/pubmed/19342300
13. Montorsi F, Wilson TG, Rosen RC, et al. Best practices in robot-assisted radical prostatectomy: recommendations of the Pasadena Consensus Panel. Eur Urol. 2012 Sep;62(3):368-81. http://www.ncbi.nlm.nih.gov/pubmed/22763081
14. Novara G, Ficarra V, Rosen RC, et al. Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. Eur Urol. 2012 Sep;62(3):431-52. http://www.ncbi.nlm.nih.gov/pubmed/22749853
15. Ficarra V, Novara G, Rosen RC, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol. 2012 Sep;62(3):405-17. http://www.ncbi.nlm.nih.gov/pubmed/22749852
16. Novara G, Ficarra V, Mocellin S, et al. Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. Eur Urol. 2012 Sep;62(3):382-404. http://www.ncbi.nlm.nih.gov/pubmed/22749851
17. Ficarra V, Novara G, Ahlering TE, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol. 2012 Sep;62(3):418-30. http://www.ncbi.nlm.nih.gov/pubmed/22749850
18. Capitanio U, Scattoni V, Freschi M, et al. Radical prostatectomy for incidental (stage T1a-T1b) prostate cancer: analysis of predictors for residual disease and biochemical recurrence. Eur Urol 2008 Jul;54(1):118-25. http://www.ncbi.nlm.nih.gov/pubmed/18314255
19. Andrèn O, Garmo H, Mucci L, et al. Incidence and mortality of incidental prostate cancer: a Swedish register-based study. Br J Cancer 2009 Jan;100(1):170-3. http://www.ncbi.nlm.nih.gov/pubmed/19088721
20. Lowe BA, Listrom MB. Incidental carcinoma of the prostate: an analysis of the predictors of progression. J Urol 1988 Dec;140(6):1340-4. http://www.ncbi.nlm.nih.gov/pubmed/3193495
21. Van Poppel H, Ameye F, Oyen R, et al. Radical prostatectomy for localized prostate cancer. Eur J Surg Oncol 1992 Oct;18(5):456-62. http://www.ncbi.nlm.nih.gov/pubmed/1426296
22. Elgamal AA, Van Poppel HP, Van de Voorde WM, et al. Impalpable invisible stage T1c prostate cancer: characteristics and clinical relevance in 100 radical prostatectomy specimens-a different view. J Urol 1997 Jan;157(1):244-50. http://www.ncbi.nlm.nih.gov/pubmed/8976263
23. Oesterling JE, Suman VJ, Zincke H, et al. PSA-detected (clinical stage T1c or B0) prostate cancer. Pathologically significant tumors. Urol Clin North Am 1993 Nov;20(4):687-93. http://www.ncbi.nlm.nih.gov/pubmed/7505977
24. Epstein JI, Walsh PC, Brendler CB. Radical prostatectomy for impalpable prostate cancer: the Johns Hopkins experience with tumors found on transurethral resection (stages T1A and T1B) and on needle biopsy (stage T1C). J Urol 1994 Nov;152(5 Pt 2):1721-9. http://www.ncbi.nlm.nih.gov/pubmed/7523719
25. Singh H, Canto EI, Shariat SF, et al. Improved detection of clinically significant, curable prostate cancer with systematic 12-core biopsy. J Urol 2004 Mar;171(3):1089-92. http://www.ncbi.nlm.nih.gov/pubmed/14767277
26. Epstein JI, Chan DW, Sokoll LJ, et al. Nonpalpable stage T1c prostate cancer: prediction of insignificant disease using free/total prostate specific antigen levels and needle biopsy findings. J Urol 1998 Dec;160(6 Pt 2):2407-11. http://www.ncbi.nlm.nih.gov/pubmed/9817393
27. Makarov DV, Trock BJ, Humphreys EB, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. Urology 2007 Jun;69(6):1095-101. http://www.ncbi.nlm.nih.gov/pubmed/17572194
28. D'Amico AV, Whittington R, Malkowicz SB, et al. Combination of preoperative PSA level, biopsy gleason score, percentage of positive biopsies and MRI T-stage to predict early PSA failure in men with clinically localized prostate cancer. Urology 2000 Apr;55(4):572-7. http://www.ncbi.nlm.nih.gov/pubmed/10736506
29. Epstein JI. Gleason score 2-4 adenocarcinoma of the prostate on needle biopsy: a diagnosis that should not be made. Am J Surg Pathol 2000 Apr;24(4):477-8. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/10757394

30. Epstein JI, Steinberg GD. The significance of low-grade prostate cancer on needle biopsy. A radical prostatectomy study of tumor grade, volume, and stage of the biopsied and multifocal tumor. Cancer 1990 Nov;66(9):1927-32.
http://www.ncbi.nlm.nih.gov:/pubmed/1699655
31. Briganti A, Larcher A, Abdollah F, et al. Updated Nomogram Predicting Lymph Node Invasion in Patients with Prostate Cancer Undergoing Extended Pelvic Lymph Node Dissection: The Essential Importance of Percentage of Positive Cores. Eur Urol 2012 Mar;61(3):480-7.
http://www.ncbi.nlm.nih.gov/pubmed/22078338
32. Schroder FH, Van den Ouden D, Davidson P. The role of surgery in the cure of prostatic carcinoma. Eur Urol Update Series 1992;1:18-23.
33. Gibbons RP. Total prostatectomy for clinically localized prostatic cancer: long-term surgical results and current morbidity. NCI Monogr 1988;(7):123-6.
http://www.ncbi.nlm.nih.gov/pubmed/3173498
34. Pound CR, Partin AW, Epstein JI, et al. Prostate-specific antigen after anatomic radical retropubic prostatectomy. Patterns of recurrence and cancer control. Urol Clin North Am 1997 May;24(2): 395-406.
http://www.ncbi.nlm.nih.gov/pubmed/9126237
35. Johansson JE, Andersson SO. Deferred treatment in localized prostatic cancer. Acta Oncol 1991;30(2):221-3.
http://www.ncbi.nlm.nih.gov/pubmed/2029410
36. Graversen PH, Nielsen KT, Gasser TC, et al. Radical prostatectomy versus expectant primary treatment in stages I and II prostatic cancer. A fifteen-year follow-up. Urology 1990 Dec;36(6):493-8.
http://www.ncbi.nlm.nih.gov/pubmed/2247914
37. Isbarn H, Wanner M, Salomon G, et al. Long-term data on the survival of patients with prostate cancer treated with radical prostatectomy in the prostate-specific antigen era. BJU Int 2010 Jul;106(1):37-43.
http://www.ncbi.nlm.nih.gov/pubmed/20002667
38. Roehl KA, Han M, Ramos CG, et al. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol 2004 Sep;172(3):910-4.
http://www.ncbi.nlm.nih.gov/pubmed/15310996
39. Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Urol Clin North Am 2001 Aug;28(3):555-65.
http://www.ncbi.nlm.nih.gov/pubmed/11590814
40. Hull GW, Rabbani F, Abbas F, et al. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol 2002 Feb;167(2 Pt 1):528-34.
http://www.ncbi.nlm.nih.gov/pubmed/11792912
41. Porter CR, Kodama K, Gibbons RP, et al. 25-year prostate cancer control and survival outcomes: a 40-year radical prostatectomy single institution series. J Urol 2006 Aug;176(2):569-74.
http://www.ncbi.nlm.nih.gov/pubmed/16813891
42. Stephenson AJ, Kattan MW, Eastham JA, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol 2009 Sep;27(26):4300-5.
http://www.ncbi.nlm.nih.gov/pubmed/19636023
43. Shao YH, Demissie K, Shih W, et al. Contemporary risk profile of prostate cancer in the United States. J Natl Cancer Inst 2009 Sep 16;101(18):1280-3.
http://www.ncbi.nlm.nih.gov/pubmed/19713548
44. Yossepowitch O, Eggener SE, Bianco FJ Jr, et al. Radical prostatectomy for clinically localized, high risk prostate cancer: critical analysis of risk assessment methods. J Urol 2007 Aug;178(2):493-9;discussion 499.
http://www.ncbi.nlm.nih.gov/pubmed/17561152
45. Hodgson D, Warde P, Gospodarowicz M. The management of locally advanced prostate cancer. Urol Oncol 1998;(4):3-12. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/21227163
46. Fallon B, Williams RD. Current options in the management of clinical stage C prostatic carcinoma. Urol Clin North Am 1990 Nov;17(4):853-66.
http://www.ncbi.nlm.nih.gov/pubmed/2219582
47. Boccon-Gibod L, Bertaccini A, Bono AV, et al. Management of locally advanced prostate cancer: a European Consensus. Int J Clin Pract 2003 Apr;57(3):187-94.
http://www.ncbi.nlm.nih.gov/pubmed/12723722

48. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 2002 Jul;360(9327):103-6.
http://www.ncbi.nlm.nih.gov/pubmed/12126818
49. Gerber GS, Thisted RA, Chodak GW, et al. Results of radical prostatectomy in men with locally advanced prostate cancer: multi-institutional pooled analysis. Eur Urol 1997;32(4):385-90.
http://www.ncbi.nlm.nih.gov/pubmed/9412793
50. Ward JF, Slezak JM, Blute ML, et al. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU Int 2005 Apr;95(6):751-6.
http://www.ncbi.nlm.nih.gov/pubmed/15794776
51. Hsu CY, Joniau S, Oyen R, et al. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. Eur Urol 2007 Jan;51(1):121-8; discussion 128-9.
http://www.ncbi.nlm.nih.gov/pubmed/16797831
52. Joniau S, Hsu CY, Lerut E, et al. A pretreatment table for the prediction of final histopathology after radical prostatectomy in clinical unilateral T3a prostate cancer. Eur Urol 2007 Feb;51(2):388-96.
http://www.ncbi.nlm.nih.gov/pubmed/16901622
53. Van Poppel H, Ameye F, Oyen R, et al. Accuracy of combined computerized tomography and fine needle aspiration cytology in lymph node staging of localized prostatic carcinoma. J Urol 1994 May;151(5):1310-14.
http://www.ncbi.nlm.nih.gov/pubmed/8158777
54. Van Poppel H, Vekemans K, Da Pozzo L, et al. Radical prostatectomy for locally advanced prostate cancer: results of a feasibility study (EORTC 30001). Eur J Cancer 2006 May;42(8):1062-7.
http://www.ncbi.nlm.nih.gov/pubmed/16624554
55. Loeb S, Smith ND, Roehl KA, et al. Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer. Urology 2007 Jun;69(6):1170-5.
http://www.ncbi.nlm.nih.gov/pubmed/17572209
56. Van Poppel H, Joniau S. An analysis of radical prostatectomy in advanced stage and high-grade prostate cancer. Eur Urol 2008 Feb;53(2):253-9.
http://www.ncbi.nlm.nih.gov/pubmed/17949893
57. D'Amico AV, Whittington R, Malkowicz SB, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. J Clin Oncol 1999 Jan;17(1):168-72.
http://www.ncbi.nlm.nih.gov/pubmed/10458230
58. Spahn M, Joniau S, Gontero P, et al. Outcome predictors of radical prostatectomy in patients with prostate-specific antigen greater than 20 ng/ml: a European multi-institutional study of 712 patients. Eur Urol 2010 Jul;58(1):1-7; discussion 10-1.
http://www.ncbi.nlm.nih.gov/pubmed/20299147
59. Gontero P, Spahn M, Tombal B, et al. Is there a prostate-specific antigen upper limit for radical prostatectomy? BJU Int 2011 Oct;108(7):1093-100.
http://www.ncbi.nlm.nih.gov/pubmed/21392220
60. Johnstone PA, Ward KC, Goodman M, et al. Radical prostatectomy for clinical T4 prostate cancer. Cancer 2006 Jun;106:2603-9.
http://www.ncbi.nlm.nih.gov/pubmed/16700037
61. Gontero P, Marchioro G, Pisani R, et al. Is radical prostatectomy feasible in all cases of locally advanced non-bone metastatic prostate cancer? Results of a single-institution study. Eur Urol 2007 Apr;51(4):922-9; discussion 929-30.
http://www.ncbi.nlm.nih.gov/pubmed/17049718
62. Ghavamian R, Bergstralh EJ, Blute ML, et al. Radical retropubic prostatectomy plus orchiectomy versus orchiectomy alone for pTxN+ prostate cancer: a matched comparison. J Urol 1999 Apr;161(4):1223-7; discussion 1277-8.
http://www.ncbi.nlm.nih.gov/pubmed/10081874
63. Messing EM, Manola J, Yao J, et al. Eastern Cooperative Oncology Group study EST 3886. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006 Jun;7(6):472-9.
http://www.ncbi.nlm.nih.gov/pubmed/16750497
64. Engel J, Bastian PJ, Baur H, et al. Survival benefit of radical prostatectomy in lymph node-positive patients with prostate cancer. Eur Urol 2010 May;57(5):754-61.
http://www.ncbi.nlm.nih.gov/pubmed/20106588

65. Steuber T, Budäus L, Walz J, et al. Radical prostatectomy improves progression-free and cancer-specific survival in men with lymph node positive prostate cancer in the prostate-specific antigen era: a confirmatory study. BJU Int 2011 Jun;107(11):1755-61.
http://www.ncbi.nlm.nih.gov/pubmed/20942833
66. Briganti A, Karnes JR, Da Pozzo LF, et al. Two positive nodes represent a significant cut-off value for cancer specific survival in patients with node positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. Eur Urol 2009 Feb;55(2):261-70.
http://www.ncbi.nlm.nih.gov/pubmed/18838212
67. Schumacher MC, Burkhard FC, Thalmann GN, et al. Good outcome for patients with few lymph node metastases after radical retropubic prostatectomy. Eur Urol 2008 Aug;54(2):344-52.
http://www.ncbi.nlm.nih.gov/pubmed/18511183
68. Briganti A, Karnes RJ, Da Pozzo LF, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. Eur Urol 2011 May;59(5):832-40.
http://www.ncbi.nlm.nih.gov/pubmed/21354694
69. Schumacher MC, Burkhard FC, Thalmann GN, et al. Is pelvic lymph node dissection necessary in patients with a serum PSA <10ng/mL undergoing radical prostatectomy for prostate cancer? Eur Urol 2006 Aug;50(2):272-9.
http://www.ncbi.nlm.nih.gov/pubmed/16632187
70. Heidenreich A, Varga Z, Von Knobloch R. Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: high incidence of lymph node metastasis. J Urol 2002 Apr;167(4):1681-6.
http://www.ncbi.nlm.nih.gov/pubmed/11912387
71. Bader P, Burkhard FC, Markwalder R, et al. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? J Urol 2003 Mar;169(3):849-54.
http://www.ncbi.nlm.nih.gov/pubmed/12576797
72. Mattei A, Fuechsel FG, Bhatta Dhar N, et al. The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodality mapping study. Eur Urol 2008 Jan;53(1):118-25.
http://www.ncbi.nlm.nih.gov/pubmed/17709171
73. Weingärtner K, Ramaswamy A, Bittinger A, et al. Anatomical basis for pelvic lymphadenectomy in prostate cancer: results of an autopsy study and implications for the clinic. J Urol 1996 Dec;156(6):1969-71.
http://www.ncbi.nlm.nih.gov/pubmed/8911367
74. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999 May;281(17):1591-7.
http://www.ncbi.nlm.nih.gov/pubmed/10235151
75. Aus G, Nordenskjöld K, Robinson D, et al. Prognostic factors and survival in nodepositive (N1) prostate cancer-a prospective study based on data from a Swedish population-based cohort. Eur Urol 2003 Jun;43(6):627-31.
http://www.ncbi.nlm.nih.gov/pubmed/12767363
76. Cheng L, Zincke H, Blute ML, et al. Risk of prostate carcinoma death in patients with lymph node metastasis. Cancer 2001 Jan;91(1):66-73.
http://www.ncbi.nlm.nih.gov/pubmed/11148561
77. Bader P, Burkhard FC, Markwalder R, et al. Is a limited lymph node dissection an adequate staging procedure for prostate cancer? J Urol 2002 Aug;168(2):514-8; discussion 518.
http://www.ncbi.nlm.nih.gov/pubmed/12131300
78. Joslyn SA, Konety BR. Impact of extent of lymphadenectomy on survival after radical prostatectomy for prostate cancer. Urology 2006 Jul;68(1):121-5.
http://www.ncbi.nlm.nih.gov/pubmed/16806432
79. Briganti A, Chun FK, Salonia A, et al. Complications and other surgical outcomes associated with extended pelvic lymphadenectomy in men with localized prostate cancer. Eur Urol 2006 Nov;50(5):1006-13.
http://www.ncbi.nlm.nih.gov/pubmed/16959399
80. Heidenreich A, Von Knobloch R, Varga Z, et al. Extended pelvic lymphadenectomy in men undergoing radical retropubic prostatectomy (RRP)-an update on >300 cases. J Urol 2004;171:312, abstract #1183.
81. Burkhard FC, Schumacher M, Studer UE. The role of lymphadenectomy in prostate cancer. Nat Clin Pract Urol 2005 Jul;2(7):336-42.
http://www.ncbi.nlm.nih.gov/pubmed/16474786

82. Vallett BS. Radical perineal prostatectomy subsequent to bilateral orchiectomy. Delaware Med J 1944;16:19-20.
83. Shelley MD, Kumar S, Wilt T, et al. A systematic review and meta-analysis of randomised trials of neoadjuvant hormone therapy for localised and locally advanced prostate carcinoma. Cancer Treat Rev 2009 Feb;35(1):9-17.
http://www.ncbi.nlm.nih.gov/pubmed/18926640
84. McLeod DG, Iversen P, See WA, et al. Casodex Early Prostate Cancer Trialists' Group. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU Int 2006 Feb;97(2):247-54.
http://www.ncbi.nlm.nih.gov/pubmed/16430622
85. Hautmann RE, Sauter TW, Wenderoth UK. Radical retropubic prostatectomy: morbidity and urinary continence in 418 consecutive cases. Urology 1994 Feb;43(2 Suppl):47-51.
http://www.ncbi.nlm.nih.gov/pubmed/8116133
86. Murphy GP, Mettlin C, Menck H, et al. National patterns of prostate cancer treatment by radical prostatectomy: results of a survey by the American College of Surgeons Commission on Cancer. J Urol 1994 Nov;152(5 Pt 2):1817-9.
http://www.ncbi.nlm.nih.gov/pubmed/7523727
87. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002 Apr;346(15):1138-44.
http://www.ncbi.nlm.nih.gov/pubmed/11948274
88. Potosky AL, Legler J, Albertsen PC, et al. Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcome Study. J Natl Cancer Inst 2000 Oct;92(19):1582-92.
http://www.ncbi.nlm.nih.gov/pubmed/11018094
89. Van Poppel H, Collette L, Kirkali Z, et al, EORTC GU Group. Quality control of radical prostatectomy: a feasibility study. Eur J Cancer 2001 May;37(7):884-91.
http://www.ncbi.nlm.nih.gov/pubmed/11313177
90. Walsh PC, Partin AW, Epstein JI. Cancer control and quality of life following anatomical radical retropubic prostatectomy: results at 10 years. J Urol 1994 Nov;152(5 Pt 2):1831-6.
http://www.ncbi.nlm.nih.gov/pubmed/7523730
91. Sofer M, Savoie M, Kim SS, et al. Biochemical and pathological predictors of the recurrence of prostatic adenocarcinoma with seminal vesicle invasion. J Urol 2003 Jan;169(1):153-6.
http://www.ncbi.nlm.nih.gov/pubmed/12478125
92. Walsh RM, Thompson IM. Prostate cancer screening and disease management: how screening may have an unintended effect on survival and mortality-the camel's nose effect. J Urol 2007 Apr;177(4):1303-6.
http://www.ncbi.nlm.nih.gov/pubmed/17382719
93. Alsikafi NF, Brendler CB. Surgical modifications of radical retropubic prostatectomy to decrease incidence of positive surgical margins. J Urol 1998 Apr;159(4):1281-5.
http://www.ncbi.nlm.nih.gov/pubmed/9507853
94. Graefen M. Is the open retropubic radical prostatectomy dead? Eur Urol 2007 Nov;52(5):1281-3. [no abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/17764828
95. Bianco FJ Jr, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology 2005 Nov;66(5 Suppl):83-94.
http://www.ncbi.nlm.nih.gov/pubmed/16194712
96. Gontero P, Kirby RS. Nerve-sparing radical retropubic prostatectomy: techniques and clinical considerations. Prostate Cancer Prostatic Dis 2005;8(2):133-9.
http://www.ncbi.nlm.nih.gov/pubmed/15711608
97. Sokoloff MH, Brendler CB. Indications and contraindications for nerve-sparing radical prostatectomy. Urol Clin North Am 2001 Aug;28(3):535-43.
http://www.ncbi.nlm.nih.gov/pubmed/11590812
98. Eichelberg C, Erbersdobler A, Haese A, et al. Frozen section for the management of intraoperatively detected palpable tumor lesions during nerve-sparing scheduled radical prostatectomy. Eur Urol 2006 Jun;49(6):1011-6; discussion 1016-8.
http://www.ncbi.nlm.nih.gov/pubmed/16546316
99. Montorsi F, Guazzoni G, Strambi LF, et al. Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. J Urol 1997 Oct;158(4):1408-10.
http://www.ncbi.nlm.nih.gov/pubmed/9302132

100. Nandipati K, Raina R, Agarwal A, et al. Early combination therapy: intracavernosal injections and sildenafil following radical prostatectomy increases sexual activity and the return of natural erections. Int J Impot Res 2006 Sep-Oct;18(5):446-51.
http://www.ncbi.nlm.nih.gov/pubmed/16482200
101. Montorsi F, Brock G, Lee J, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol 2008 Oct;54(4): 924-31.
http://www.ncbi.nlm.nih.gov/pubmed/18640769
102. Padma-Nathan H, McCullough AR, Levine LA, et al. Study Group. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res 2008 Sep-Oct;20(5):479-86.
http://www.ncbi.nlm.nih.gov/pubmed/18650827

10. TREATMENT: DEFINITIVE RADIOTHERAPY

10.1 Introduction

There have been no randomised studies comparing RP with either external-beam radiotherapy (EBRT) or brachytherapy for localised PCa. The National Institutes of Health (NIH) consensus statement in 1988 (1) stated that external irradiation offers the same long-term survival results as surgery; moreover, EBRT provides a quality of life (QoL) at least as good as that following surgery (2). A more recent systematic review has provided a more sophisticated overview of outcomes from reports that meet the criteria for stratifying patients by risk group, standard outcome measures, numbers of patients, and minimum median follow-up period (3). Radiotherapy continues to be an important and valid alternative to surgery as the sole form of curative therapy.

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for external-beam radiotherapy, and all centres that are unable to offer this should have a plan to introduce it as a routine method for the definitive treatment of prostate cancer.

In addition to external irradiation, transperineal low-dose or high-dose rate brachytherapy are widely used. In localised and locally advanced PCa, several randomised phase III trials conducted by the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) have established the indications for the combination of external irradiation and ADT.

Whatever the technique used, the choice of treatment - after the appropriate assessment of the extent of the tumour - must be based on a multidisciplinary approach and should take the following into account:

- 2009 TNM classification.
- Gleason score, defined using an adequate number of core biopsies (at least 12).
- Baseline prostate-specific antigen (PSA).
- Age of the patient.
- Patient's comorbidity, life expectancy, and QoL.
- International Prostate Symptom Score (IPSS) and uroflowmetry recordings.
- National Comprehensive Cancer Network (NCCN) and/or D'Amico prognostic factor classification (4).

Additional information on the various aspects of radiotherapy in the treatment of PCa is available in an extensive published overview (5).

10.2 Technical aspects: three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated external-beam radiotherapy (IMRT)

Anatomic data acquired by scanning the patient in a treatment position are transferred to the three-dimensional treatment planning system, which visualises the clinical target volume and then adds a surrounding safety margin. Real-time verification of the irradiation field by means of portal imaging allows comparison of the treated and simulated fields, and correction of deviations where displacement is more than 5 mm. Three-dimensional CRT improves local control through dose escalation, without significantly increasing the risk of morbidity.

It is possible to use IMRT with linear accelerators equipped with the latest multileaf collimators and specific software. At the time of irradiation, a multileaf collimator automatically - and in the case of IMRT continuously - adapts to the contours of the target volume seen by each beam; this allows for a more complex distribution of the dose to be delivered within the treatment field and provides concave isodose curves, which are particularly useful as a means of sparing the rectum. To date, no randomised trials have been published

comparing dose escalation using IMRT and 3D-CRT.

With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of IGRT, in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear (6).

Another evolving technique for the delivery of IMRT is tomotherapy, which uses a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning. Preliminary data suggest that this technique is feasible in PCa treatment (7).

Whatever the techniques and their degree of sophistication, quality assurance plays a major role in the management of radiotherapy, requiring the involvement of physicians, physicists, dosimetrists, radiographers, radiologists, and computer scientists.

10.3 Radiotherapy for localised prostate cancer

10.3.1 ***Dose escalation***

Before the advent of 3D-CRT, radiotherapy doses to the prostate were usually in the order of 64 Gy in 2-Gy fractions, or equivalent. With 3D-CRT, and more recently IMRT, dose escalation beyond this limit has been possible. Several randomised studies have shown that dose escalation (range 76-80 Gy) has a significant impact on the 5-year survival without biochemical relapse (8-14). These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant hormone therapy (see below) has varied.
To date, no trials have yet shown that dose escalation results in an OS benefit, but the trials have shown a remarkable consistency in that they have all reported improvements in freedom from biochemical progression in patients treated with dose-escalated radiotherapy:

- The M.D. Anderson study compared 78 Gy with 70 Gy conventional radiotherapy. It included 305 stage T1-3 patients with a pre-treatment PSA level of more than 10 ng/mL, with a median follow-up period of 9 years. At 10 years after treatment, 16% of the high-risk patients treated with 70 Gy had died of disease, in comparison with 4% of patients treated with 78 Gy (P = 0.05), a percentage similar to that for patients with higher PSA values, 15% vs. 2% (P = 0.03) (8).
- The PROG 95-09 study evaluated 393 T1b-T2b patients, 75% of whom had a Gleason score ≤ 6 and a PSA level < 15 ng/mL. The patients were randomly assigned to receive an initial boost to the prostate alone, using conformal protons, of either 19.8 Gy or 28.8 Gy, and then 50.4 Gy to a larger volume. With a median follow-up period of 8.9 years, there was a significant difference in the 10-year American Society for Radiation Oncology (ASTRO) biochemical failure rate, at 32.4% for conventional-dose treatment (70.2 Gy) and 16.7% for high-dose treatment (79.2 Gy) (P < 0.0001). The difference persisted when only low-risk patients (58% of the total) were examined: 28.2% for conventional and 7.1% for high-dose treatment (P < 0.0001) (9).
- The MRC RT01 study, comparing a dose of 64 Gy with 74 Gy, both with neoadjuvant hormonal therapy, in 843 men with T1b-T3b disease, showed an 11% difference in the 5-year biochemical disease-free survival (BDFS) in favour of dose-escalated radiotherapy (P = 0.0007) (15).
- The Dutch randomised phase III trial comparing 68 Gy with 78 Gy showed a significant increase in the 5-year rate of freedom from clinical or biochemical failure in patients treated with a higher dose of radiotherapy (P = 0.02) (11).
- The phase III trial of the French Federation of Cancer Centres compared 70 Gy with 80 Gy in men with localised prostate cancer, in 306 patients with a pelvic lymph node involvement risk of < 10% (Partin) or pN0, with no hormonal therapy allowed before, during, or after radiotherapy. With a median follow-up period of 61 months, better 5-year biological outcomes were seen in favor of dose-escalated radiotherapy (P = 0.036) (12).

In everyday practice, a minimum dose of ≥ 74 Gy is recommended for EBRT + hormone therapy (expert opinion). Currently, it is not possible to make different recommendations by risk group, as there is evidence from these randomised trials for an impact of dose-escalation in low-risk, medium-risk, and high-risk patients, although probably of different magnitudes (10).

10.3.2 ***Neoadjuvant or adjuvant hormone therapy plus radiotherapy***

Several randomised trials have shown clearly that in at least some patients with nonmetastatic prostate cancer, radiotherapy alone is inferior to the combination of radiotherapy plus ADT:

- EORTC study 22863 recruited 415 patients diagnosed with T1-2 grade 3 World Health Organization (WHO) or T3-4 N0 M0 and any histological grade, and compared radiotherapy plus adjuvant ADT with radiotherapy alone. Androgen deprivation treatment was allowed in cases of relapse. A total of 82% of patients were diagnosed as T3, 10% as T4, and 89% as N0. Hormonal treatment consisted of oral cyproterone acetate (CPA) 50 mg three times daily for 1 month, beginning 1 week before the start of radiotherapy, and goserelin acetate (Zoladex), 3.6 mg subcutaneously every 4 weeks for 3

years, starting on the first day of radiotherapy. The pelvic target volume received was 50 Gy, and the prostatic target volume was 20 Gy. With a median follow-up period of 66 months, the combination therapy compared with radiotherapy alone yielded significantly better survival (78% vs. 62%; P = 0.001) (16). At a median follow-up of 9.1 years, the 10-year OS remained significantly higher at 58.1% versus 39.8% (P < 0.0001), as did the clinical PFS at 47.7% vs. 22.7% (P < 0.0001). The 10-year cumulative incidences of PCa mortality were 11.1% vs. 31% (P < 0.0001), and the 10-year cumulative incidences of cardiovascular mortality were 11.1% vs. 8.2% (P = 0.75) (17).

- RTOG study 8531 recruited 977 patients diagnosed with T3-4 N0-1 M0, or pT3, after RP. Androgen deprivation therapy was begun in the last week of irradiation and continued up to relapse (Group I) or was started at recurrence (Group II). A total of 15% of patients in Group I and 29% in Group II had undergone RP, and 14% of patients in Group I and 26% in Group II were pN1. Goserelin acetate, 3.6 mg subcutaneously, was administered every 4 weeks. The pelvis was irradiated with 45 Gy, while the prostatic bed received 20-25 Gy. Patients diagnosed with stage pT3 received 60-65 Gy. With a median follow-up time of 7.6 years for all patients, the 10-year OS was significantly greater for the adjuvant arm, at 49% vs. 39% (P = 0.002) (18).
- RTOG study 86-10 included 471 patients with bulky (5 × 5 cm) tumours T2-4 N0-X M0. Androgen deprivation therapy was administered at 2 months before irradiation and during irradiation, or in the case of relapse in the control arm. Thirty-two percent of the patients were diagnosed as having T2, 70% as having T3-4, and 91% with N0. The hormone treatment consisted of oral flutamide (Eulexin), 250 mg three times daily, and goserelin acetate (Zoladex), 3.6 mg every 4 weeks by subcutaneous injection. The pelvic target volume received 45 Gy and the prostatic target volume received 20-25 Gy. The 10-year OS estimates were 43% for ADT plus irradiation vs. 34% for hormonal treatment, although the difference was not significant (P = 0.12). There was a significant improvement in the 10-year disease-specific mortality (23% vs. 36%; P = 0.01), disease-free survival (11% vs. 3%; P < 0.0001) and in the biochemical failure rate (65% vs. 80%; P < 0.0001), with the addition of ADT having no statistical impact on the risk of fatal cardiac events (19).
- A phase III randomised trial including 206 patients with a PSA level of at least 10 ng/mL (maximum 40 ng/mL), a Gleason score of at least 7 (range 7-10), or radiographic evidence of extra-prostatic disease, compared 3D-CRT alone or in combination with 6 months of ADT. After a median follow-up period of 7.6 years, intermediate-risk or high-risk patients without moderate or severe comorbidity who had been randomly assigned to receive 3D-CRT + ADT showed a 13% improvement in the OS rate (P < 0.001) (20).
- The RTOG 94-08 trial, including 1979 patients with T1b-T2b and PSA < 20 ng/mL, showed that adding a complete androgen blockade for 2 months before and 2 months during conventional lower-dose radiotherapy (66 Gy) significantly improved the 10-year OS rate (62% vs. 57%; P = 0.03) (13).These trials included patients with a wide range of clinical risk factors, most of whom were thought to be at high risk of disease progression, usually by virtue of their clinical stage, but in some instances because of their PSA level or Gleason grade. The most powerful conclusion from these studies comes from the EORTC 22863 study, which is the basis for the combination of radiotherapy and ADT in patients with locally advanced (T3-T4) nonmetastatic prostate cancer. Whether these results should be applied to patients with all stages of prostate cancer is unclear.
- EORTC trial 22991, comparing 3D-CRT with or without IMRT with a choice of three levels of dosage (70 Gy, 74 Gy, or 78 Gy), with or without 6 months of neoadjuvant and concomitant hormonal therapy, was closed in April 2008 after recruiting 800 patients; the results are awaited.

10.3.2.1 Duration of adjuvant or neoadjuvant ADT in combination with radiotherapy.

Several phase III trials have attempted to define the optimum timing and/or duration of ADT in combination with radiotherapy.

- The EORTC-22961 randomised phase III trial, comparing 36 months of hormonal treatment plus radiotherapy with 6 months of hormonal treatment plus radiotherapy in 970 patients, showed that increased hormonal treatment improved OS in patients with high-risk PCa after 5 years (14). The 5-year overall mortality rates for short-term and long-term suppression were 19.0% and 15.2%, respectively; the observed hazard ratio was 1.42 (upper 95.71% confidence limit, 1.79; P = 0.65 for non-inferiority).
- The Trans-Tasman Oncology Group (TROG) randomised trial compared no neoadjuvant ADT with 3 months or 6 months of neoadjuvant ADT with goserelin and flutamide starting 2 months before radiotherapy, or 6 months of ADT with the same regimen starting 5 months before RT, in 818 men with T2b-T4 N0 M0 prostate cancer. While 3 months of ADT improved the biochemical PFS in comparison with radiotherapy alone, 6 months additionally improved the prostate cancer-specific survival and OS (21).

- The RTOG 94-13 randomised trial used a 2 × 2 design comparing whole-pelvic with prostate-only radiotherapy (see below) and neoadjuvant with adjuvant ADT in 1323 patients with stages T1c-T4 N0 M0 prostate cancer, and found no differences in the PFS. The report does, however, describe possible interactions between the timing of ADT and the radiotherapy volume, in subgroup analyses (22).
- The RTOG 92-02 study compared 4 months of neoadjuvant ADT (2 months before and during radiotherapy) with the same plus an additional 24 months of adjuvant ADT in 1554 men with T2c-T4 prostate cancer and reported improvements in local progression, disease-free survival, biochemical survival, and metastasis-free survival in patients treated with additional adjuvant ADT. However, an OS benefit was restricted to men with a Gleason score of 8-10 in the subgroup analysis (23).

10.3.2.2 Combined dose-escalated RT and ADT

Zelefsky et al. (24) reported a retrospective analysis of 2251 patients with T1-3 N0-X M0 PCa consisting of 571 low-risk patients (22.4%), 1074 intermediate-risk patients (42.1%), and 906 high-risk patients (35.5%), according to the National Comprehensive Cancer Network classification. Three-dimensional conformal radiotherapy or IMRT were administered to the prostate and seminal vesicles only. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last 10 years using image-guided IMRT. Androgen deprivation therapy by complete androgen blockade with a luteinising hormone-releasing hormone (LHRH) agonist plus oral antiandrogen was administered, at the discretion of the treating physician, to 1249 patients (49%), including 623 high-risk patients (69%), 456 intermediate-risk patients (42%), and 170 low-risk (30%) patients. The duration of ADT was 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before radiotherapy and continued during radiotherapy. The end points were 10-year biochemical disease-free survival and distant metastasis-free survival. With an 8-year median follow-up period, the 10-year biochemical disease-free survival in each risk group was significantly improved by dose escalation: 84% (> 75.6 Gy) vs. 70% for low-risk patients (P = 0.04), 76% (> 81 Gy) vs. 57% for intermediate- risk patients (P = 0.0001), and 55% (> 81 Gy) vs. 41% for high-risk patients (P = 0.0001). The 6-month ADT also influenced the biochemical disease-free survival in intermediate-risk and high-risk patients, with 55% vs. 36% for high-risk patients (P < 0.0001). In the multivariate analysis, a dose greater than 81 Gy (P = 0.027) and ADT (P = 0.052) were found to be significant predictive factors for distant metastasis-free survival, but none of these parameters influenced PCa mortality or OS. There were very low rates of grade 3-4 acute or late toxicity (25).

10.3.2.3 Proposed EBRT treatment policy for localised prostate cancer

Low risk. Intensity-modulated radiotherapy with escalated dose and without androgen deprivation therapy is an alternative to brachytherapy (see below).

Intermediate risk. In patients who are suitable for ADT, combined IMRT with short-term ADT (4-6 months) (26,27). In patients who are unsuitable for ADT (e.g., due to comorbidities) or unwilling to accept it (e.g., to preserve their sexual health), IMRT at an escalated dose (80 Gy) or a combination of IMRT and brachytherapy is recommended.

High risk *(T1-2 N0-X M0 with either a baseline PSA value > 20 ng/mL and/or a Gleason score of 8-10) plus short-term ADT, suggested by the Boston and 94-08 RTOG trials, did not show any impact on OS in the high-risk cohort.* The high risk of relapse outside the irradiated volume makes a combined modality approach mandatory, consisting of dose-escalated IMRT including the pelvic lymph nodes plus long-term ADT. The duration of ADT has to take into account WHO performance status, comorbidities, and the number of poor prognostic factors: cT stage (> T2c), Gleason score 8-10, and PSA > 20 ng/mL.

10.3.3 ***The role of radiotherapy in locally advanced PCa: T3-4 N0, M0***

The incidence of locally advanced PCa has declined as a result of individual and mass screening. Pelvic lymph node irradiation is optional for N0 patients, but the results of radiotherapy alone are very poor (28). The randomised trials discussed above clearly established that, in patients with locally advanced disease who are treated with radiotherapy, the addition of ADT results in better outcomes. However, some clinicians considered that the benefits were due to the earlier use of ADT and questioned the benefits of radiotherapy itself in this context. Three trials have established that in locally advanced disease, radiotherapy is effective and that combined radiotherapy plus ADT is clearly superior to ADT alone.

The National Cancer Institute of Canada (NCIC)/UK Medical Research Council (MRC)/Southwest Oncology Group (SWOG) intergroup PR3/PR07 study included 1,205 patients with T3-4 (n = 1057) or T2, PSA > 40 ng/mL (n = 119), or T2, PSA > 20 ng and Gleason > 8 (n = 25) and N0-X M0 PCa, who were randomly assigned to lifelong ADT (bilateral orchidectomy or LHRH agonist), with or without radiotherapy (65-70 Gy to the prostate, with or without 45 Gy to the pelvic lymph nodes). With a median follow-up period of 6 years, the

addition of RT to ADT reduced the risk of death from any cause by 23% (P = 0.03) and the risk of death due to PCa by 46% (P = 0.0001) (29,30).

The Groupe d'Etude des Tumeurs Uro-Génitales (GETUG) trial included 273 patients with locally advanced PCa T3-4 or pT3 N0 M0, who were randomly assigned to lifelong ADT using an LHRH agonist (leuprorelin), with or without RT (70 Gy to the prostate plus 48 ± 2 Gy to the pelvic lymph nodes). With a median follow-up period of 67 months, there was a significant improvement in the 5-year disease free survival (P < 0.001), metastatic disease-free survival (P < 0.018), and locoregional PFS (P < 0.0002), but the effect on OS was not reported (31).

The SPCG-7/SFUO-3 randomised study (32) compared hormonal treatment alone (i.e., 3 months of continuous androgen blockade followed by continuous flutamide treatment (n = 439) with the same treatment combined with radiotherapy (n = 436). After a median follow-up period of 7.6 years, the 10-year cumulative incidences for prostate cancer-specific mortality were 23.9% and 11.9%, respectively (95% confidence interval, 4.9 to 19.1%), and the 10-year cumulative incidences for overall mortality were 39.4% in the hormonal treatment-only group and 29.6% in the hormonal treatment plus radiotherapy group (95% CI, 0.8 to 18%).

10.3.4 ***The benefits of lymph node irradiation in prostate cancer***

10.3.4.1 Prophylactic irradiation of pelvic lymph nodes in high-risk localised PCa

Invasion of the pelvic lymph nodes is a poor prognostic factor and makes systemic medical treatment mandatory, since radiotherapy alone is insufficient (14). There is no firm evidence base for prophylactic whole-pelvic irradiation, since randomised trials have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic lymph nodes in high-risk cases. Such studies include the RTOG 77 06 study, including 484 patients with T1b-T2 (33), the Stanford study with only 91 patients (34), and the GETUG 01 trial, which included 444 patients with T1b-T3 N0 pNx M0 (35). In the RTOG 94-13 study (22), there were no differences in the PFS in patients treated with whole-pelvic or prostate-only radiotherapy, but interactions between whole-pelvic radiotherapy and the duration of ADT were reported following the subgroup analysis. Pelvic lymphadenectomy may be needed to improve the selection of patients who may be able to benefit from pelvic lymph node irradiation and to supplement the use of Partin's tables (36) and/or the Roach formula (37). The results of pelvic lymphadenectomy, particularly in young patients, will enable radiation oncologists to tailor both the planning target volume and the duration of ADT: specifically, no pelvic irradiation for pN0 patients, but pelvic irradiation for pN1 patients with long-term ADT. The benefits of pelvic nodal irradiation at a high dosage using IMRT merit further investigation in a phase II trial. One such trial is currently recruiting through the RTOG, while a second is in randomised phase II in the United Kingdom.

10.3.4.2 Very high-risk PCa: c or pN1, M0

Patients with pelvic lymph node involvement lower than the iliac regional nodes who are younger than 80 years old, with a WHO performance status 0-1 and no severe comorbidity, may be candidates for EBRT plus immediate long-term hormonal treatment. The RTOG 85-31 randomised phase III trial, with a median follow-up period of 6.5 years, showed that 95 of the 173 pN1 patients who received pelvic radiotherapy with immediate hormonal therapy had better 5-year (54%) and 9-year (10%) PFS rates (PSA < 1.5 ng/mL) vs. 33% and 4%, respectively, with radiation alone and hormonal manipulation instituted at the time of relapse (P < 0.0001). The multivariate analysis showed that this combination had a statistically significant impact on the OS, disease-specific failure, metastatic failure and biochemical control rates (38). The GETUG 12 trial has addressed the impact of neoadjuvant chemotherapy with docetaxel on the PFS in a cohort of 413 high-risk patients, defined as having one or more of the following criteria: T3-4, Gleason score ≥ 8, PSA ≥ 20 ng/mL, pN+. Patients were randomly assigned to either goserelin 10.8 mg every 3 months for 3 years, plus four cycles of docetaxel, 70 mg/m^2 every 3 weeks, plus estramustine 10 mg/kg/dL on days 1-5 (arm 1); or goserelin alone (arm 2). Local therapy was administered at 3 months and consisted of RT in 358 patients (87%). Toxicity included grade 3-4 neutropenia (27%) with neutropenic fever in 2%, but no toxicity-related death and no secondary leukemia. With a median follow-up period of 4.6 years, the 4-year PFS was 85% in arm 1 in comparison with 81% in arm 2 (P = 0.26), but the data need to mature (39).

10.4 Proton beam and carbon ion beam therapy

In theory, proton beams are an attractive alternative to photon-beam radiotherapy for PCa, as they deposit almost all their radiation dose at the end of the particle's path in tissue (the Bragg peak), in contrast to photons, which deposit radiation along their path. There is also a very sharp fall-off for proton beams beyond their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In contrast, photon beams continue to deposit energy until they leave the body, including an exit dose.

In practice, however, this has the disadvantage that dose distributions from protons are highly sensitive to changes in internal anatomy, such as might occur with bladder or rectal filling, and prostate proton therapy is usually delivered with lateral beams. It is also possible that high linear energy transfer (LET)

radiotherapy using protons or carbon ions might offer inherent biological advantages over photons, which have a greater capacity for DNA damage dose for dose.

Only one randomised trial has incorporated proton therapy in one arm: the Loma Linda/Massachusetts General Hospital trial compared standard-dose conformal radiotherapy with dose-escalated radiotherapy using protons for the boost dose (9). This trial cannot, however, be used as evidence for the superiority of proton therapy per se, as its use here could be viewed simply as a sophisticated method of dose escalation. A randomised trial comparing equivalent doses of proton-beam therapy with IMRT is needed in order to compare the efficacy of protons vs. photons; a study of this type is under consideration by the RTOG.

Two recent planning studies comparing conformal proton therapy with IMRT have yielded conflicting results; one study suggested that the two are equivalent in terms of rectal dose sparing, but that IMRT is actually superior in terms of bladder sparing (40); the other study suggested a clearer advantage for protons (41). Further studies are clearly needed. Meanwhile, proton therapy must be regarded as a promising, but experimental, alternative to photon-beam therapy. Theoretically, proton therapy may be associated with a lower risk of secondary cancers in comparison with IMRT because of the lower integral dose of radiation, but there are no data from patients treated for PCa to support this.

Carbon ions offer similar theoretical advantages to those of protons as an alternative to photon-beam therapy. In a phase II study, 175 patients with T1-3, N0-1, M0 PCa were treated with carbon ions at a dosage equivalent to 66 Gy in 20 fractions over 5 weeks (42). The treatment appeared to be well tolerated, with no RTOG grade 3 or 4 bowel or genitourinary toxicity, and an overall 4-year biochemical disease-free rate (BDFR) of 88% (41). As with protons, a randomised trial comparing carbon ions with IMRT and using equivalent doses is required.

10.5 Transperineal brachytherapy

Transperineal brachytherapy is a safe and effective technique. There is a consensus on the following eligibility criteria:

- Stage cT1b-T2a N0, M0.
- A Gleason score ≤ 6 assessed on an adequate number of random biopsies.
- An initial PSA level of ≤ 10 ng/mL.
- ≤ 50% of biopsy cores involved with cancer.
- A prostate volume of < 50 $cm^{3.}$
- An International Prostatic Symptom Score (IPSS) ≤ 12 (43).

Patients with low-risk PCa are the most suitable candidates for low-dose-rate (LDR) brachytherapy. Further guidelines on the technical aspects of brachytherapy have been published recently and are strongly recommended (44).

In 1983, Holm et al. described the transperineal method with endorectal sonography, in which the patient is positioned in a dorsal decubitus gynaecological position (45). Implantation is undertaken with the patient under general anaesthesia or spinal block, and involves a learning curve for the whole team: the surgeon for delineation of the prostate and needle placement, the physicist for real-time dosimetry, and the radiation oncologist for source loading. The sonography probe introduced into the rectum is fixed in a stable position.

There have been no randomised trials comparing brachytherapy with other curative treatment modalities, and outcomes are based on nonrandomised case series. The results of permanent implants have been reported from different institutions, with a median follow-up ranging from 36 to 120 months (46). The recurrence-free survival after 5 and 10 years has been reported to range from 71% to 93% and from 65% to 85%, respectively (47-54). A significant correlation has been shown between the implanted dose and recurrence rates (55). Patients receiving a D90 of > 140 Gy had a significantly higher biochemical control rate (PSA < 1.0 ng/mL) after 4 years than patients who received less than 140 Gy (92% vs. 68%). There is no benefit from adding neoadjuvant or adjuvant ADT to LDR brachytherapy (46).

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), post-implantation transurethral resection of the prostate (TURP; required in up to 8.7% of cases), and incontinence (0-19%) (56). A small randomised trial has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity (57). This observation requires further study in a larger number of patients. Chronic urinary morbidity can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Previous TURP for benign prostatic hyperplasia increases the risk of post-implantation incontinence and urinary morbidity.

The incidence of grade III toxicity is less than 5%. Erectile dysfunction develops in about 40% of the patients after 3-5 years. In a recent retrospective analysis of 5,621 men who had undergone LDR brachytherapy (58), the urinary, bowel, and erectile morbidity rates were 33.8%, 21%, and 16.7%, respectively, with invasive procedure rates of 10.3%, 0.8%, and 4%, respectively.

In patients with permanent implants, iodine-125 in granular form is the radioactive element of

reference, while palladium-103 may be used for less differentiated tumours with a high doubling time. The doses delivered to the planning target volume are 144 Gy for iodine-125 and 125 Gy for palladium-103. A Gleason score of 7 is still a "grey area," but patients with a Gleason score of 4 + 3 showed no difference in outcome (59).

A small randomised trial has suggested that using stranded rather than loose seeds is associated with better seed retention and less seed migration, and this should be the standard choice (60).

In cases of intermediate-risk or high-risk localised PCa, brachytherapy in combination with supplemental external irradiation (61) or neoadjuvant hormonal treatment (62) may be considered. The optimum dose of supplemental EBRT is unclear. A randomised trial comparing 44 Gy with 20 Gy of EBRT plus palladium-103 brachytherapy closed early, showing no difference in the biochemical outcomes (63).

Nonpermanent transperineal interstitial prostate brachytherapy using a high-dose-rate iridium-192 stepping source and a remote afterloading technique can be applied with a total dose of 12-20 Gy in two to four fractions, combined with fractionated external radiotherapy of 45 Gy (64). Higher doses of supplemental EBRT than this may best be delivered with IMRT; a report from Memorial Sloan-Kettering indicates that this approach is safe and feasible (65).

Recent data suggest an equivalent outcome in terms of the BDFS in comparison with high-dose EBRT (HD-EBRT) (66). In a retrospective analysis of modern series (67,68), BDFS rates of 85.8%, 80.3%, and 67.8% in men with low-risk, intermediate-risk, and high-risk PCa, respectively, were reported after a mean follow-up of 9.43 years. Quality-of-life changes are similar with high-dose EBRT and high-dose-rate (HDR) brachytherapy, in terms of diarrhoea and insomnia (69). However, the frequency of erectile dysfunction was significantly increased with HDR brachytherapy (86% vs. 34%). A single randomised trial of EBRT vs. EBRT plus HDR brachytherapy has been reported (70). A total of 220 patients with organ-confined PCa were randomised to EBRT alone with a dose of 55 Gy in 20 fractions, or EBRT with a dose of 35.75 Gy in 13 fractions, followed by HDR brachytherapy with a dose of 17 Gy in two fractions over 24 hours. In comparison with EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in the biochemical relapse-free survival (P = 0.03). There were no differences in the rates of late toxicity. Patients randomly assigned to EBRT plus brachytherapy had a significantly better QoL as measured by their Functional Assessment of Cancer Therapy-Prostate (FACT-P) score at 12 weeks. However, a very high, uncommon rate of early recurrences was observed in the EBRT arm alone, even after 2 years, possibly due to the uncommon fractionation used (70). There is still a need to compare dose-escalated EBRT plus hormone therapy, with the same followed by a brachytherapy boost, in intermediate-risk and high-risk patients.

For T1-2 N0 M0 disease, the 5-year biochemical failure rates are similar for permanent seed implantation, high-dose (> 72 Gy) external radiation, combination seed/external irradiation, and radical prostatectomy, according to a study of 2991 patients diagnosed with T1-2 consecutive localised PCa treated between 1990 and 1998 at the Cleveland Clinic Foundation and Memorial Sloan-Kettering Cancer Center, with a minimum follow-up period of 1 year (66).

10.6 Late toxicity

Patients must be informed about the potential late genitourinary or gastrointestinal toxicity that may occur, and also about the impact of irradiation on erectile function. Late toxicity was analysed using a dose of 70 Gy in prospective EORTC randomised trial 22863 (1987-1995) (71), in which 90% of patients were diagnosed as having stage T3-4. A total of 377 patients (91%) out of 415 enrolled were evaluable for long-term toxicity, graded according to a modified RTOG scale. Eighty-six patients (22.8%) had grade ≥ 2 urinary or intestinal complications or leg oedema, 72 of whom had grade 2 (moderate) toxicity, while 10 had grade 3 (severe) toxicity and four died due to grade 4 (fatal) toxicity. Although four (1%) late treatment-related deaths occurred, the long-term toxicity was limited, with a grade 3 or 4 late complication rate of less than 5% being reported (Table 17). These data can be used as a baseline for comparison with irradiation techniques currently in use, such as 3D-CRT and IMRT.

Table 17: Incidence of late toxicity by Radiation Therapy Oncology Group (RTOG) grade (from EORTC trial 22863)

Toxicity	Grade 2		Grade 3		Grade 4		Any significant toxicity (≥ grade 2)	
	n	%	n	%	n	%	n	%
Cystitis	18	4.7	2	0.5	0	0	20	5.3
Haematuria	18	4.7	0	0	0	0	18	4.7
Urinary stricture	18	4.7	5	1.3	4	1	27	7.1
Urinary incontinence	18	4.7	2	0.5	0	0	20	5.3
Overall GU toxicity	**47**	**12.4**	**9**	**2.3**	**4†**	**1†**	**60**	**15.9**
Proctitis	31	8.2	0	0	0	0	31	8.2
Chronic diarrhoea	14	3.7	0	0	0	0	14	3.7
Small bowel obstruction	1	0.2	1	0.2	0	0	2	0.5
Overall GI toxicity	**36**	**9.5**	**1**	**0.2**	**0**	**0**	**37**	**9.8**
Leg oedema	**6**	**1.5**	**0**	**0**	**0**	**0**	**6**	**1.5**
Overall toxicity*	**72**	**19.0**	**10**	**2.7**	**4**	**1**	**86**	**22.8**

GI = gastrointestinal; GU = genitourinary.

** Overall toxicity included GU and GI toxicity and leg oedema. As most patients had more than one type of toxicity, the overall toxicity does not result from simple addition.*

† Two of the grade 4 patients were irradiated with cobalt-60.

Note: there was no other significant (≥ grade 2) toxicity among patients irradiated with cobalt-60 (n = 15), except for two patients with grade 4 GU (stated above) and only one patient with grade 2 GI toxicity.

Radiotherapy affects erectile function to a lesser degree than surgery, according to retrospective surveys of patients (2). A recent meta-analysis has shown that the 1-year rates of probability for maintaining erectile function were 0.76 after brachytherapy, 0.60 after brachytherapy + external irradiation, 0.55 after external irradiation, 0.34 after nerve-sparing radical prostatectomy, and 0.25 after standard radical prostatectomy.

When studies with more than 2 years of follow-up were selected (i.e., excluding brachytherapy), the rates became 0.60, 0.52, 0.25, and 0.25, respectively, with a greater spread between the radiation techniques and surgical approaches (72).

Recent studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT (73,74). In a retrospective evaluation of 30,552 and 55,263 men who had undergone either EBRT or RP, the risk of being diagnosed with rectal cancer increased 1.7-fold in comparison with the surgery group (73). Another analysis (74) showed that the relative risk of developing bladder cancer increased by 2.34-fold in comparison with a healthy control population. On the other hand, a re-analysis of SEER data including more than 100,000 patients demonstrated a risk of about 0.16% (i.e., 160 cases per 100,000 patients) of radiation-induced malignant tumours (75).

Corresponding data on late toxicity have also been reported by the Memorial Sloan-Kettering Cancer Center group, from their experience in 1571 patients with T1-T3 disease treated with either 3D-CRT or IMRT at doses of between 66 Gy and 81 Gy, with a median follow-up of 10 years (75). Both acute gastrointestinal and genitourinary toxicity appeared to be predictive for corresponding late toxicity. The overall rate of NCIC/Common Toxicity Criteria (CTC) grade 2 or more gastrointestinal toxicity was 5% with IMRT, in comparison with 13% with 3D-CRT. The incidence of grade 2 or higher late genitourinary toxicity was 20% in patients treated with 81 Gy, in comparison with 12% in patients treated with lower doses. The overall incidence of grade 3 gastrointestinal toxicity was 1%, and grade 3 genitourinary toxicity was 3%. These data suggest that IMRT can successfully protect against late gastrointestinal toxicity, but, interestingly, with dose escalation, genitourinary toxicity may become the predominant type of morbidity (76).

10.6.1 Immediate (adjuvant) postoperative external irradiation after radical prostatectomy

Extracapsular invasion (pT3), Gleason score ≥ 7, and positive surgical margins (R1) are associated with a risk of local recurrence, which can be as high as 50% after 5 years (77,78).Three prospective randomised trials have assessed the role of immediate postoperative radiotherapy (adjuvant radiotherapy, ART). EORTC study 22911 (79), with a target sample size of 1005 patients, compared immediate postoperative radiotherapy (60 Gy) with radiotherapy delayed until local recurrence (70 Gy) in patients classified as having pT3 pN0 with risk

factors R1 and pT2R1 after retropubic RP. Immediate postoperative radiotherapy proved to be well tolerated. Grade 4 toxicity was not observed. The grade 3 genitourinary toxicity rate was 5.3%, in comparison with 2.5% in the observation group after 10 years. For patients younger than 70, the study concluded that immediate postoperative radiotherapy after surgery significantly improved the 10-year biological PFS: 60.6% vs. 41.1%. A difference observed in the clinical progression rates for the entire cohort that favoured ART after 5 years was not sustained after 10 years, although locoregional control was better in the long-term follow-up after immediate irradiation (hazard ratio, HR = 0.45, P < 0.0001). However, ART patients with pT2-3 R1 also showed an improved clinical PFS after 10 years (HR = 0.69; P = 0.008). Overall survival did not differ significantly between the treatment arms. After re-evaluation using a central pathological review, the highest impact of ART was found to be on the biochemical progression (HR down to 0.3) seen in patients with positive margins, but there was also a positive effect of 10% after 5 years for pT3 with negative margins and other risk factors (80,81).

The most suitable candidates for immediate radiotherapy may be those with multifocal positive surgical margins and a Gleason score > 7. The conclusions of ARO trial 96-02 (n = 385) appear to support those of the EORTC study. After a median follow-up period of 54 months, the radiotherapy group demonstrated a significant improvement in biochemical PFS of 72% vs. 54%, respectively (P = 0.0015). However - of major interest, and in contrast to other studies - randomisation of the patients was carried out after they had achieved an undetectable PSA level following RP (< 0.1 ng/mL), and only pT3 tumours were included. This finding indicates that adjuvant radiotherapy works even in the setting of an undetectable PSA after RP and additional risk factors (81). Conversely, the updated results, with a median follow-up of more than 12 years, of the SWOG 8794 trial, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved the metastasis-free survival, with a 10-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, P = 0.016) and a 10-year OS of 74% vs. 66% (median: 1.9 years prolongation; P = 0.023) (82).

Thus, for patients classified as pT3 pN0 with a high risk of local failure after RP due to positive margins (highest impact), capsule rupture, and/or invasion of the seminal vesicles, who present with a PSA level of < 0.1 ng/mL, two options can be offered in the framework of informed consent:

Either immediate adjuvant radiotherapy (ART) to the surgical bed (81-83,86) after recovery of urinary function
Or
clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL (84,85).

10.6.2 ***Delayed (salvage) postoperative external irradiation after radical prostatectomy***

Early SRT provides a possibility of cure for patients with an increasing or persistent PSA after RP. More than 60% of patients who are treated before the PSA level rises to more than 0.5 ng/mL will achieve an undetectable PSA level again (84,85), thus providing patients with an approximately 80% chance of being progression-free 5 years later (85). A retrospective analysis based on 635 patients who underwent RP in 1982-2004, followed up through December 2007, who experienced biochemical and/or local recurrence and received no salvage treatment (n = 397) or salvage radiotherapy alone (n = 160) within 2 years of biochemical recurrence, showed that SRT was associated with a threefold increase in the PCa-specific survival relative to those who received no salvage treatment (P < 0.001). Salvage radiotherapy has also been effective in patients with a rapid PSA doubling time (87). So far, the optimal SRT dose has not been well defined. It should be at least 66 Gy. However, more recent data suggest that higher total doses can achieve higher rates of biochemical control at 3-5 years (88,89). In a systematic review, the pre-SRT PSA level and SRT dose were correlated with biochemical recurrence, showing that the outcome improved by 2.6% per 0.1 ng/mL PSA and by 2% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA (90,91).

The role of an additional ADT in combination with SRT remains controversial. The RTOG 9601 randomised, multicentre phase III trial was designed to compare antiandrogen therapy (bicalutamide monotherapy 150 mg/dL) plus SRT (n = 387) with a placebo plus SRT alone (n = 383) in men with pT3 (n = 518)/ pT2 R1 (n = 252) N0 M0 prostate cancer, with an elevated PSA after surgery. The median follow-up period in surviving patients was 7.1 years. The addition of 24 months of peripheral and androgen blockade during and after RT significantly improved freedom from PSA progression, at 57% vs. 40% (P < 0.0001), and reduced the incidence of metastatic PCa (7.4% versus 12.6%; P < 0.04), without adding significantly to radiation toxicity. Longer follow-up periods are required in order to assess the significance of the benefit in OS and to provide an analysis of risk-stratified subsets (91).

These two approaches, together with the efficacy of neoadjuvant hormone therapy, are currently being compared in three prospectively randomised clinical trials: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) in the United Kingdom, the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES), and Groupe d'Etude

des Tumeurs Uro-Génitales (GETUG) 17/0702. The role of short-term hormone therapy in combination with radiotherapy is being investigated in the European Organization for Research and Treatment of Cancer (EORTC) 22043 randomised trial.

Decision-making on whether to proceed with adjuvant RT for high risk PCa - pT3-4 pN0 M0 with undetectable PSA - after radical prostatectomy, or to postpone RT as an early salvage procedure in case of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before radical prostatectomy that adjuvant radiotherapy may be administered if the patient has negative prognostic risk factors. Ultimately, the decision on whether to treat requires a multidisciplinary approach that takes into account the optimal timing of radiotherapy when it is used and provides justification when it is not, and this will help the discussion between the physician and the patient.

10.7 Guidelines for definitive radiotherapy

	LE	GR
In localised prostate cancer, T1c-T2c N0 M0, 3D-CRT with or without IMRT is recommended, even for young patients who decline surgical intervention.	1b	B
For high-risk patients, long-term ADT before and during radiotherapy is recommended, as it results in increased overall survival.	2a	B
In patients with locally advanced prostate cancer (T3-4, N0 M0), who are fit enough to receive EBRT, the recommended treatment is EBRT plus long-term ADT and the use of ADT alone is inappropriate.	1b	A
In patients with cT1-T2a, Gleason score < 7 (or 3 + 4), PSA ≤ 10 ng/mL, prostate volume ≤ 50 mL, without a previous TURP and with a good IPSS, transperineal interstitial brachytherapy with permanent implants can be an alternative.	2a	B
In patients with pathological tumour stage T3 N0 M0, immediate postoperative external irradiation after RP may improve the biochemical and clinical disease-free survival, with the highest impact in cases of positive margins.	1b	A
In patients with pathological tumour stage T2-3 N0 M0, salvage irradiation is indicated in case of persisting PSA or biochemical failure, but before the PSA level rises above 0.5 ng/mL.	3	B
In patients with locally advanced prostate cancer, T3-4 N0 M0, concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external-beam irradiation for patients with WHO 0-2 performance status, is recommended, as it improves the overall survival.	1b	A
In a subset of patients with T2c-T3 N0-X and a Gleason score of 2-6, short-term ADT before and during radiotherapy can be recommended, as it may favourably influence the overall survival.	1b	A
In patients with very high-risk prostate cancer, c-pN1 M0, with no severe comorbidity, pelvic external irradiation and immediate long-term adjuvant hormonal treatment is recommended, as it will improve the overall survival, disease-specific failure rate, metastatic failure rate, and biochemical control.	2b	B

CRT = conformal radiotherapy; IMRT = intensity-modulated radiotherapy; ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; PSA = prostate specific antigen; TYRP = transurethral resection of the prostate; IPSS = international prostatic symptom score; RP = radical prostatectomy; TURP = International Prostatic Symptom Score.

10.8 References

1. Consensus statement: the management of clinically localized prostate cancer. National Institutes of Health Consensus Development Panel (no authors listed). NCI Monogr 1988;(7):3-6. [No abstract available]
   http://www.ncbi.nlm.nih.gov/pubmed/3050539
2. Fowler FJ, Barry MJ, Lu-Yao G, et al. Outcomes of external beam radiation therapy for prostate cancer: a study of Medicare beneficiaries in three surveillance epidemiology and end results areas. J Clin Oncol 1996 Aug;14(8):2258-65.
   http://www.ncbi.nlm.nih.gov/pubmed/8708715
3. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. BJU Int 2012 Feb;109 Suppl 1:22-9
   http://www.ncbi.nlm.nih.gov/pubmed/22239226
4. NCCN Clinical Practice guidelines in Oncology Prostate Cancer, Version a.2013 (no archive for the old version? 4.2011.
   http://www.nccn.org/clinical.asp [accessed February 8th, 2013]

5. Nilsson S, Norlen BJ, Widmarks A. A systematic overview of radiation therapy effects in prostate cancer. Acta Oncol 2004;43(4):316-81.
http://www.ncbi.nlm.nih.gov/pubmed/15303499
6. Ling CC, Yorke E, Fuks Z. From IMRT to IGRT: frontierland or neverland? Radiother Oncol 2006 Feb;78(2):119-22.
http://www.ncbi.nlm.nih.gov/pubmed/16413622
7. Keiler L, Dobbins D, Kulasekere R, et al. Tomotherapy for prostate adenocarcinoma: a report on acute toxicity. Radiother Oncol 2007 Aug;84(2):171-6.
http://www.ncbi.nlm.nih.gov/pubmed/17692975
8. Kuban DA, Levy LB, Cheung MR, et al. Long-term failure patterns and survival in a randomized dose- escalation trial for prostate cancer. Who dies of disease? Int J Radiat Oncol Biol Phys 2011 Apr 1;79(5):1310-7.
http://www.ncbi.nlm.nih.gov/pubmed/20493642
9. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol 2010 Mar 1;28(7):1106-11.
http://www.ncbi.nlm.nih.gov/pubmed/20124169
10. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. Int J Radiat Oncol Biol Phys 2009 Aug;74(5):1405-18.
http://www.ncbi.nlm.nih.gov/pubmed/19616743 69
11. Peeters ST, Heemsbergen WD, Koper PCM, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 2006 May;24(13):1990-6.
http://www.ncbi.nlm.nih.gov/pubmed/16648499
12. Beckendorf V, Guerif S, Le Prisé E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2011 Jul 15;80(4):1056-63.
http://www.ncbi.nlm.nih.gov/pubmed/21147514
13. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011 Jul 14;365(2):107-18.
http://www.ncbi.nlm.nih.gov/pubmed/21751904
14. Bolla M, de Reijke TM, Van Tienhoven G, et al. EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med. 2009 Jun 11;360(24):2516-27.
http://www.ncbi.nlm.nih.gov/pubmed/19516032
15. Dearnaley DP, Sydes MR, Graham JD, et al. RT01 collaborators. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomized controlled trial. Lancet Oncol 2007 Jun;8(6):475-87.
http://www.ncbi.nlm.nih.gov/pubmed/17482880
16. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. Lancet 2002 Jul;360(9327):103-6.
http://www.ncbi.nlm.nih.gov/pubmed/12126818
17. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010 Nov;11(11):1066-73.
http://www.ncbi.nlm.nih.gov/pubmed/20933466
18. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys 2005 Apr 1;61(5):1285-90.
http://www.ncbi.nlm.nih.gov/pubmed/15817329
19. Roach M, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long term results of RTOG 8610. J Clin Oncol 2008 Feb;26(4):585-91.
http://www.ncbi.nlm.nih.gov/pubmed/18172188
20. D"Amico A, Renshaw AA, Loffredo M, et al. Androgen suppression and radiation vs radiation alone for prostate cancer; a randomized controlled trial. JAMA 2008 Jan;299(3):289-95.
http://www.ncbi.nlm.nih.gov/pubmed/18212313

21 Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial.Lancet Oncol 2011 May;12(5):451-9
http://www.ncbi.nlm.nih.gov/pubmed/21440505

22. Lawton CA, DeSilvio M, Roach M 3rd, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. Int J Radiat Oncol Biol Phys. 2007 Nov 1;69(3):646-55.
http://www.ncbi.nlm.nih.gov/pubmed/17531401

23. Hanks GE, Pajak TF, Porter A, et al. Radiation Therapy Oncology Group. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol 2003 Nov 1;21(21):3972-8.
http://www.ncbi.nlm.nih.gov/pubmed/14581419

24. Zelefsky MJ, Pei X, Chou JF, et al. Dose escalation for prostate cancer radiotherapy: predictors of Long-term biochemical tumor control and distant metastases-free survival outcomes. Eur Urol 2011 Dec;60(6):1133-9.
http://www.ncbi.nlm.nih.gov/pubmed/21889832

25. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of later rectal and urinary toxicities after three dimensional conformal radiotherapy and intensity modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008 Mar;70(4):1124-9.
http://www.ncbi.nlm.nih.gov/pubmed/18313526

26. Krauss D, Kestin L, Ye H, et al. A Lack of benefit for the addition of androgen deprivation therapy to dose-escalated radiotherapy in the treatment of intermediate- and high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2011 Jul 15;80(4):1064-71
http://www.ncbi.nlm.nih.gov/pubmed/20584576

27. Kupelian PA, Ciezki J, Reddy CA, et al. Effect of increasing radiation doses on local and distant failures in patients with localized prostate cancer. Int J Radiat Oncol Biol Phys 2008 May;71(1):16-22.
http://www.ncbi.nlm.nih.gov/pubmed/17996382

28. Leibel SA, Fuks Z, Zelefsky MJ, et al. The effects of local and regional treatments on the metastatic outcome in prostatic carcinoma with pelvic lymph node involvement. Int J Radiat Oncol Biol Phys 1994 Jan;28(1):7-16.
http://www.ncbi.nlm.nih.gov/pubmed/8270461

29. Warde, P, Mason, M, Ding, K, et al and for the NCIC CTG PR.3/MRC UK PR07 investigators. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet 2012 Dec 17;378(9809):2104-11.
http://www.ncbi.nlm.nih.gov/pubmed/22056152

30. Mason M, Warde P, Sydes M, et al. The National Cancer Institute of Canada Clinical Trials Group PR3/; Medical Research Council PR07 Trial Management Group. Defining the need for local therapy in locally advanced prostate cancer: an appraisal of the MRC PR07 study. Clin Oncol (R Coll Radiol) 2005 Jun;17(4):217-8. [No abstract available]
http://www.ncbi.nlm.nih.gov/pubmed/15997913

31. Mottet N, Peneau M, Mazeron J, et al. Impact of radiotherapy (RT) combined with androgen deprivation (ADT) versus ADT alone for local control in clinically locally advanced prostate cancer. Proc Am Soc Clin Oncol 2010;28;abstr CRA4505
http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=49013

32. Widmark A, Klepp O, Solberg A, et al for the Scandinavian Prostate Cancer Group Study, the Swedish Association for Urological Oncology. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomized phase III trial. Lancet 2008 Jan;373(9660):301-8.
http://www.ncbi.nlm.nih.gov/pubmed/19091394

33. Leibel SA, Fuks Z, Zelefsky MJ, et al. The effects of local and regional treatments on the metastatic outcome in prostatic carcinoma with pelvic lymph node involvement. Int J Radiat Oncol Biol Phys 1994 Jan;28(1):7-16.
http://www.ncbi.nlm.nih.gov/pubmed/8270461

34. Asbell SO, Krall JM, Pilepich MV, et al. Elective irradiation in stage A2, B carcinoma of the prostate: analysis of RTOG 77 06. Int J Radiation Oncology Biol Phys 1988 Dec;15(6):1307-16.
http://www.ncbi.nlm.nih.gov/pubmed/3058656

35. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. J Clin Oncol 2007 Dec;25(34):5366-73. http://www.ncbi.nlm.nih.gov/pubmed/18048817
36. Partin AW, Kattan MW, Subong EN, et al. Combination of prostate-specific antigen, clinical stage and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. JAMA 1997 May;277(18):1445-51. http://www.ncbi.nlm.nih.gov/pubmed/9145716
37. Roach M, Marquez C, Yuo H, et al. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 1993 Jan;28(1):33-7. http://www.ncbi.nlm.nih.gov/pubmed/7505775
38. Lawton CA, Winter K, Grignon D, et al. Androgen suppression plus radiation versus radiation alone for patients with D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on a national prospective randomized trial, RTOG 85-31. J Clin Oncol 2005 Feb;23(4):800-7. http://www.ncbi.nlm.nih.gov/pubmed/15681524
39. Fizazi K, Lesaunier F, Delva R, et al. Docetaxel-estramustine in high-risk localized prostate cancer: first results of the French Genitourinary Tumor Group phase III trial (GETUG12) J Clin Oncol 2011;2 http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=102&abstractID=77102 9 (suppl; abstr 4513).
40. Trofimov A, Nguyen PL, Coen JJ, et al. Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. Int J Radiat Oncol Biol Phys 2007 Oct;69(2):444-53. http://www.ncbi.nlm.nih.gov/pubmed/17513063
41. Vargas C, Fryer A, Mahajan C, et al. Dose-volume comparison of proton therapy and intensity modulated radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2008 Mar;70(3):744-51. http://www.ncbi.nlm.nih.gov/pubmed/17904306
42. Ishikawa H, Tsuji H, Kamada T, et al. Working Group for Genitourinary Tumors. Carbon ion radiation therapy for prostate cancer: results of a prospective phase II study. Radiother Oncol 2006 Oct;81(1):57-64. http://www.ncbi.nlm.nih.gov/pubmed/16971008
43. Ash D, Flynn A, Batterman J, et al. ESTRA/EAU Urological Brachytherapy Group; EORTC Radiotherapy Group. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. Radiother Oncol 2000 Dec;57(3):315-21. http://www.ncbi.nlm.nih.gov/pubmed/11104892
44. Salembier C, Lavagnini P, Nickers P, et al. GEC ESTRO PROBATE Group. Tumour and target volumes in permanent prostate brachytherapy: a supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy. Radiother Oncol 2007 Apr;83(1):3-10. http://www.ncbi.nlm.nih.gov/pubmed/17321620
45. Holm HH, Juul N, Pedersen JF, et al. Transperineal seed implantation in prostatic cancer guided by transrectal ultrasonography. J Urol 1983 Aug;130(2):283-6. http://www.ncbi.nlm.nih.gov/pubmed/6876274
46. Machtens S, Baumann R, Hagemann J, et al. Long-term results of interstitial brachytherapy (LDR brachytherapy) in the treatment of patients with prostate cancer. World J Urol 2006 Aug;24(3):289-95. http://www.ncbi.nlm.nih.gov/pubmed/16645877
47. Grimm PD, Blasko JC, Sylvester JE, et al. 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. Int J Radiat Biol Phys 2001 Sep;51(1):31-40. http://www.ncbi.nlm.nih.gov/pubmed/11516848
48. Potters L, Klein EA, Kattan MW, et al. Monotherapy for stage T1-T2 prostate cancer: radical prostatectomy, external beam radiotherapy, or permanent seed implantation. Radiother Oncol 2004 Apr;71(1):29-33. http://www.ncbi.nlm.nih.gov/pubmed/15066293
49. Sylvester JE, Blasko JC, Grimm R, et al. Fifteen year follow-up of the first cohort of localized prostate cancer patients treated with brachytherapy. J Clin Oncol 2004 Apr;22(14S):4567. http://meeting.jco.org/cgi/content/abstract/22/14_suppl/4567
50. Potters L, Morgenstern C, Calugaru E, et al. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. J Urol 2005 May;173(5):1562-6. http://www.ncbi.nlm.nih.gov/pubmed/15821486
51. Stone NN, Stock RG, Unger P. Intermediate term biochemical-free progression and local control following 125iodine brachytherapy for prostate cancer. J Urol 2005 Mar;173(3):803-7. http://www.ncbi.nlm.nih.gov/pubmed/15711273

52. Zelefsky MJ, Kuban DA, Levy LB, et al. Multi-institutional analysis of long-term outcome for stages T1-T2 prostate cancer treated with permanent seed implantation. Int J Radiat Oncol Biol Phys 2007 Feb;67(2):327-33.
http://www.ncbi.nlm.nih.gov/pubmed/17084558
53. Lawton CA, DeSilvio M, Lee WR, et al. Results of a phase II trial of transrectal ultrasound-guided permanent radioactive implantation of the prostate for definitive management of localized adenocarcinoma of the prostate (RTOG 98-05). Int J Radiat Oncol Biol Phys 2007 Jan;67(1):39-47.
http://www.ncbi.nlm.nih.gov/pubmed/17084551
54. Potters L, Morgenstern C, Calugaru E, et al. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. J Urol 2008 May;179(5Suppl.): S20-S24.
http://www.ncbi.nlm.nih.gov/pubmed/18405743
55. Stock RG, Stone NN. Importance of post-implant dosimetry in permanent brachytherapy. Eur Urol 2002 Apr;41(4):434-9.
http://www.ncbi.nlm.nih.gov/pubmed/12074816
56. Budäus L, Bolla M, Bossi A, et al. Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. Eur Urol 2012 Jan;61(1):112-27
http://www.ncbi.nlm.nih.gov/pubmed/22001105
57. Elshaikh MA, Ulchaker JC, Reddy CA, et al. Prophylactic tamsulosin (Flomax) in patients undergoing prostate 125I brachytherapy for prostate carcinoma: final report of a double-blind placebo-controlled randomized study. Int J Radiat Oncol Biol Phys 2005 May;62(1):164-9.
http://www.ncbi.nlm.nih.gov/pubmed/15850917
58. Chen AB, D"Amico AV, Neville BA, et al. Patient and treatment factors associated with complications after prostate brachytherapy. J Clin Oncol 2006 Nov;24(33):5298-304.
http://www.ncbi.nlm.nih.gov/pubmed/17114664
59. Merrick GS, Butler WM, Galbreath RW, et al. Biochemical outcome for hormone naive patients with Gleason score 3+4 versus 4+3 prostate cancer undergoing permanent prostate brachytherapy. Urology 2002 Jul;60(1):98-103.
http://www.ncbi.nlm.nih.gov/pubmed/12100932
60. Reed DR, Wallner KE, Merrick GS, et al. A prospective randomized comparison of stranded vs. loose 125I seeds for prostate brachytherapy. Brachytherapy 2007 Apr;6(2):129-34.
http://www.ncbi.nlm.nih.gov/pubmed/17434106
61. Potters L, Cha C, Ashley R, et al. Is pelvic radiation necessary in patients undergoing prostate brachytherapy? Int J Radiat Oncol Biol Phys 1998;42:300 (abstract 2146).
62. Lee LN, Stock RG, Stone NN. Role of hormonal therapy in the management of intermediate-to high-risk prostate cancer treated with permanent radioactive seed implantation. Int J Radiat Oncol Biol Phys 2002 Feb;52(2):444-52.
http://www.ncbi.nlm.nih.gov/pubmed/11872291
63. Wallner K, Merrick G, True L, et al. 20 Gy versus 44 Gy supplemental beam radiation with Pd-103 prostate brachytherapy: preliminary biochemical outcomes from a prospective randomized multicenter trial. Radiother Oncol 2005 Jun;75(3):307-10.
http://www.ncbi.nlm.nih.gov/pubmed/16086912
64. Galalae RM, Kovacs G, Schultze J, et al. Long term outcome after elective irradiation on the pelvic lymphatics and local dose escalation using high dose rate brachytherapy for locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 2002 Jan;52(1):81-90.
http://www.ncbi.nlm.nih.gov/pubmed/11777625
65. Zelefsky MJ, Nedelka MA, Arican ZL, et al. Combined brachytherapy with external beam radiotherapy for localized prostate cancer: reduced morbidity with an intraoperative brachytherapy planning technique and supplemental intensity-modulated radiation therapy. Brachytherapy 2008 Jan-Mar;7(1):1-6.
http://www.ncbi.nlm.nih.gov/pubmed/18299108
66. Kupelian PA, Potters L, Ciezki JP, et al. Radical prostatectomy, external beam radiotherapy < 72 Gy, external radiotherapy > or = 72 Gy, permanent seed implantation or combined seeds/external beam radiotherapy for stage T1-2 prostate cancer. Int J Radiat Oncol Biol Phys 2004 Jan;58(1):25-33.
http://www.ncbi.nlm.nih.gov/pubmed/14697417
67. Sylvester JE, Grimm PD, Blasko JC, et al. 15-year biochemical relapse free survival in clinical stage T1-T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. Int J Radiat Oncol Biol Phys 2007 Jan;67(1):57-64.
http://www.ncbi.nlm.nih.gov/pubmed/17084544

68. Phan TP, Syed AM, Puthawala A, et al. High dose rate brachytherapy as a boost for the treatment of localized prostate cancer. J Urol 2007 Jan;177(1):123-7.
http://www.ncbi.nlm.nih.gov/pubmed/17162020
69. Vordermark D, Wulf J, Markert K, et al. 3-D conformal treatment of prostate cancer to 74 Gy vs high dose rate brachytherapy boost: a cross-sectional quality of life survey. Acta Oncol 2006;45(6):708-16.
http://www.ncbi.nlm.nih.gov/pubmed/16938814
70. Hoskin PJ, Motohashi K, Bownes P, et al. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. Radiother Oncol 2007 Aug;84(2):114-20.
http://www.ncbi.nlm.nih.gov/pubmed/17531335
71. Ataman F, Zurlo A, Artignan X, et al. Late toxicity following conventional radiotherapy for prostate cancer: analysis of the EORTC trial 22863. Eur J Cancer 2004 Jul;40(11):1674-81.
http://www.ncbi.nlm.nih.gov/pubmed/15251156
72. Robinson JW, Moritz S, Fung T. Meta-analysis of rates of erectile function after treatment of localized prostate carcinoma. Int J Radiat Oncol Biol Phys 2002 Nov;54(4):1063-8.
http://www.ncbi.nlm.nih.gov/pubmed/12419432
73. Baxter NN, Trepper JE, Durham SB, et al. Increased risk of rectal cancer after prostate radiation: a population-based study. Gastroenterology 2005 Apr;128(4):819-24.
http://www.ncbi.nlm.nih.gov/pubmed/15825064
74. Liauw SL, Sylvester JE, Morris CG, et al. Second malignancies after prostate brachytherapy: incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up. Int J Radiat Oncol Biol Phys 2006 Nov;66(3):669-73.
http://www.ncbi.nlm.nih.gov/pubmed/16887293
75. Abdel-Wahab M, Reis IM, Hamilton K. Second primary cancer after radiotherapy for prostate cancer-a SEER analysis of brachytherapy versus external beam radiotherapy. Int J Radiat Oncol Biol Phys 2008 Sep;71(1):58-68.
http://www.ncbi.nlm.nih.gov/pubmed/18374503
76. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008 Mar;70(4):1124-9.
http://www.ncbi.nlm.nih.gov/pubmed/18313526
77. Hanks GE. External-beam radiation therapy for clinically localized prostate cancer: patterns of care studies in the United States. NCI Monogr 1988;(7):75-84.
http://www.ncbi.nlm.nih.gov/pubmed/3050542
78. Swanson GP, Thompson IM. Adjuvant radiotherapy for high-risk patients following radical prostatectomy. Urol Oncol 2007 Nov-Dec;25(6):515-19..
http://www.ncbi.nlm.nih.gov/pubmed/18047963
79. Bolla M, van Poppel H, Tombal B, et al. European Organisation for Research and Treatment of Cancer, Radiation Oncology and Genito-Urinary Groups. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012 Dec 8;380(9858):2018-27.
http://www.ncbi.nlm.nih.gov/pubmed/23084481
80. Van der Kwast TH, Bolla M, Van Poppel H, et al. EORTC 22911. Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy: EORTC 22911. J Clin Oncol 2007 Sep 20;25(27):4178-86.
http://www.ncbi.nlm.nih.gov/pubmed/17878474
81. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009 Jun 20;27(18):2924-30.
http://www.ncbi.nlm.nih.gov/pubmed/19433689
82. Swanson GP, Thompson IM, Tangen C, et al. Update of SWOG 8794: adjuvant radiotherapy for pT3 prostate cancer improves metastasis free survival. Int J Rad Oncol Biol Phys 2008;72:S31.
83. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009 Mar;181(3):956-62.
http://www.ncbi.nlm.nih.gov/pubmed/19167731
84. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007 May;25:2035-41.
http://www.ncbi.nlm.nih.gov/pubmed/17513807

85. Siegmann A, Bottke D, Faehndrich J et al. Salvage radiotherapy after prostatectomy - What is the best time to treat? Radiother Oncol. 2012 May;103(2):239-43.
http://www.ncbi.nlm.nih.gov/pubmed/22119375
86. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012 Dec 8;380(9858):2018-27.
http://www.ncbi.nlm.nih.gov/pubmed/23084481
87. Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA 2008 Jun;299:2760-9.
http://www.ncbi.nlm.nih.gov/pubmed/18560003
88. King CR, Kapp DS. Radiotherapy after prostatectomy: is the evidence for dose escalation out there? Int J Radiat Oncol Biol Phys 2008 Jun;71(2):346-50.
http://www.ncbi.nlm.nih.gov/pubmed/18234451
89. Siegmann A, Bottke D, Faehndrich J, et al. Dose escalation for patients with decreasing PSA during radiotherapy for elevated PSA after radical prostatectomy improves biochemical progression-free survival: results of a retrospective study. Strahlenther Onkol 2011 Aug;187(8):467-72.
http://www.ncbi.nlm.nih.gov/pubmed/21786112
90. King CR. The timing of salvage radiotherapy after radical prostatectomy: a systematic review. Int J Radiat Oncol Biol Phys 2012 Sep;84(1):104-11.
http://www.ncbi.nlm.nih.gov/pubmed/22795730
91. Shipley WU, Hunt D, Lukka H, et al. Initial report of RTOG 9601: A phase III trial in prostate cancer: Antiandrogen therapy with bicalutamide during and after radiation therapy improves freedom from progression and reduces the incidence of metastatic disease in patients following radical prostatectomy with pT2-3, N0 disease, and elevated PSA levels (abstract). Int J Radiat Biol Phys 2010;s27.
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=104&abstractID=72161

11. EXPERIMENTAL LOCAL TREATMENT OF PROSTATE CANCER

11.1 Background

Besides radical prostatectomy (RP), external beam radiation and/or brachytherapy, cryosurgical ablation of the prostate (CSAP) and high-intensity focused ultrasound (HIFU) have emerged as alternative therapeutic options in patients with clinically localised PCa (1-4).

Although HIFU is still considered to be an experimental treatment, CSAP has been recognised as a true therapeutic alternative according to the guidelines of the American Urological Association. Both HIFU and CSAP have been developed as minimally invasive procedures, which have potentially the same therapeutic efficacy as established surgical and non-surgical options, with reduced therapy-associated morbidity.

11.2 Cryosurgery of the prostate (CSAP)

Cryosurgery uses freezing techniques to induce cell death by:

- dehydration resulting in protein denaturation;
- direct rupture of cellular membranes by ice crystals;
- vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemia;
- apoptosis (1-4).

Freezing of the prostate is ensured by placement of 12-15 17G-cryoneedles under TRUS guidance, placement of thermosensors at the level of the external sphincter and bladder neck, and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance, resulting in a temperature of -40°C in the mid-gland and at the neurovascular bundle.

*11.2.1 **Indication for CSAP***

Patients who are ideal candidates for CSAP are those who have organ-confined PCa and those identified as

having minimal tumour extension beyond the prostate (1-3). The prostate should be < 40 mL in size. Prostate glands > 40 mL should be hormonally downsized to avoid any technical difficulty in placing cryoprobes under the pubic arch. PSA serum levels should be < 20 ng/mL, and the biopsy Gleason score should be < 7. It is important that patients with a life expectancy > 10 years should be fully informed that there are no data, or only minimal data, on the long-term outcome for cancer control at 10 and 15 years.

*11.2.2 **Results of modern cryosurgery for PCa***

When comparing treatment modalities, it is important to bear in mind that, in modern RP patients with clinically organ-confined PCa, there is a very low risk (2.4%) of dying from PCa at 10 years after surgery (5). Therapeutic results have improved over time with enhanced techniques, such as gas-driven probes and transperineal probe placement, as used in third-generation cryosurgery (6-11).

An objective assessment of PSA outcome is not easily performed because some institutions use PSA values < 0.1 ng/mL as an indicator of therapeutic success, whereas others use the American Society of Therapeutic Radiology and Oncology (ASTRO) criteria, which requires three consecutive increases in PSA level.

With regard to second-generation CSAP, if a PSA nadir < 0.5 ng/mL is used, biochemical disease-free survival (BDFS) at 5 years is 60% and 36% for low-risk and high-risk patients, respectively (6,7).

Long et al. (6) have performed a retrospective analysis of the multicentre, pooled, CSAP results of 975 patients stratified into three risk groups. Using PSA thresholds of 1.0 ng/mL and < 0.5 ng/mL at a mean follow-up of 24 months, the 5-year actuarial BDFS rate was:

- 76% and 60%, respectively, for the low-risk group;
- 71% and 45%, respectively, for the intermediate-risk group;
- 61% and 36%, respectively, for the high-risk group.

However, according to a recent meta-analysis of 566 cryosurgery-related publications, there were no controlled trials, survival data or validated biochemical surrogate end-points available for analysis (12).

Cryosurgery showed progression-free survival (PFS) of 36-92% (projected 1- to 7-year data), depending on risk groups and the definition of failure. Negative biopsies were seen in 72-87% of cases, but no biopsy data were available for the currently used third-generation cryotherapy machines.

With regard to third-generation cryosurgery, clinical follow-up is short, with a 12-month PSA follow-up carried out in only 110/176 (63%) patients (6-11). Eighty of these (73%) patients still had a PSA nadir < 0.4 ng/mL, whereas 42/65 (64.6%) low-risk patients remained free from biochemical progression using the 0.4 ng/mL cut-off.

Longer follow-up has been reported by Bahn et al. (9), who have analysed the therapeutic results of 590 patients undergoing CSAP for clinically localised and locally advanced PCa. At a PSA cut-off level of < 0.5 ng/mL, the 7-year BDFS for low-, medium- and high-risk groups was 61%, 68% and 61%, respectively.

Nerve-sparing cryosurgery, as reported recently (13), must still be considered an experimental therapeutic option. Nerve-sparing surgery was performed in nine patients with unilateral PCa confirmed on repeated biopsies; CSAP was carried out on the side of the positive biopsy, whereas the negative biopsy side was spared from freezing.

*11.2.3 **Complications of CSAP for primary treatment of PCa***

Erectile dysfunction occurs in about 80% of patients and remains a consistent complication of the CSAP procedure, independent of the generation of the system used. The complication rates described in third generation cryosurgery include tissue sloughing in about 3%, incontinence in 4.4%, pelvic pain in 1.4% and urinary retention in about 2% (6-11). The development of fistula is usually rare, being < 0.2% in modern series. About 5% of all patients require transurethral resection of the prostate (TURP) for subvesical obstruction.

Quality of life and sexuality following CSAP have been investigated in a clinical phase II trial recruiting 75 men (14). Quality-of-life analysis by the prostate-specific FACT-P questionnaire showed that most subscales return to pre-treatment levels by 12 months after CSAP. Furthermore, no significant changes are seen when comparing data at 36 months with those at 12 months. With regard to sexuality, 37% of men were able to have intercourse 3 years after CSAP.

In a recent, prospective, randomised clinical trial, 244 men with newly diagnosed organ-confined PCa were randomised to receive either external beam radiation therapy (EBRT) or to undergo CSAP (15). After a follow-up of 3 years, sexual function was significantly less impaired in the EBRT group.

11.2.4 ***Summary conclusions for CSAP***

Patients with low-risk PCa (PSA < 10 ng/mL, < T2a, Gleason score < 6) or intermediate-risk PCa (PSA > 10 ng/mL, or Gleason score > 7, or stage > 2b) represent potential candidates for CSAP.
Prostate size should be < 40 mL at the time of therapy.
Long-term results are lacking, whereas 5-year BDFS rates are inferior to those achieved by RP in low-risk patients. Patients must be informed accordingly.

11.3 HIFU of the prostate

HIFU consists of focused ultrasound waves emitted from a transducer, which cause tissue damage by mechanical and thermal effects as well as by cavitation (16). The goal of HIFU is to heat malignant tissues above 65°C so that they are destroyed by coagulative necrosis.

HIFU is performed under general or spinal anaesthesia, with the patient lying in the lateral position. The procedure is time-consuming, with about 10 g prostate tissue treated per hour.

In a 2006 review, 150 papers related to HIFU were identified and evaluated with regard to various oncological and functional outcome parameters (12). No controlled trial was available for analysis, and no survival data were presented. No validated biochemical, surrogate end-point was available for HIFU therapy.

11.3.1 ***Results of HIFU in PCa***

As with CSAP, it appears to be difficult to interpret oncological outcome in patients undergoing HIFU because various PSA thresholds are defined, and no international consensus exists on objective response criteria. The results of HIFU are limited, with outcome data from < 1,000 PCa cases published in the literature.

According to the review mentioned above (12), HIFU showed PFS (based on PSA ± biopsy data) of 63-87% (projected 3- to 5-year data), but median follow-up in the studies ranged from 12-24 months only.

In one of the largest single-centre studies, 227 patients with clinically organ-confined PCa were treated with HIFU, and their outcome data were analysed after a mean follow-up of 27 months (range: 12-121 months) (17). The projected 5-year BDFS was 66%, or only 57% if patients had exhibited a pre-therapeutic PSA value of 4-10 ng/mL. Incontinence and bladder neck stricture decreased over time from 28% and 31% to 9% and 6%, respectively. In one of the studies (18), a significant decrease in pre-treatment PSA serum levels from 12 to 2.4 ng/mL was observed. However, 50% of the 14 patients demonstrated positive prostate biopsies during follow-up. In another study (19), a complete response rate (i.e., PSA < 4 ng/mL) and six negative biopsies were achieved in 56% of the patients.

Thüroff *et al*. (19) have summarised the efficacy results of a European multicentre study comprising the data of 559 patients with mainly low- and intermediate-risk PCa, and have reported a negative biopsy rate of 87.2% in 288 men with a follow-up of at least 6 months. A PSA nadir after 6 months' follow-up could be determined in 212 patients, and was 1.8 ng/mL. However, following the initial procedure, it could be demonstrated that the PSA nadir might be reached in 12-18 months.

Blana *et al*. have reported the results of 146 patients undergoing HIFU with a mean follow-up of 22.5 months (20). The mean PSA level at initiation of therapy was 7.6 ng/mL; the PSA nadir achieved after 3 months was 0.07 ng/mL. However, after 22 months, the median PSA level was 0.15 ng/mL. Of the 137 men available for analysis, 93.4% demonstrated a negative control biopsy. The PSA nadir appeared to be strongly associated with treatment failure (21) ($P < 0.001$). Patients with a PSA nadir of 0.0-0.2 ng/mL had a treatment failure rate of only 11% compared with 46% in patients with a PSA nadir of 0.21-1.00 ng/mL, and 48% with a PSA nadir of > 1.0 ng/mL. Recently, the group has updated its results, with a total of 163 men treated for clinically organ-confined PCa. Within the 4.8 ± 1.2 years of follow-up, the actuarial DFS rate at 5 years was 66%, with salvage treatment initiated in 12% of patients (22).

In another study, 517 men with organ-confined or locally advanced PCa were treated with HIFU (23). Biochemical failure was defined as the PSA nadir + 2 ng/mL, according to the Phoenix guidelines with regard to radiotherapy. After a median follow-up of 24 months, the BDFS was 72% for the entire cohort. The BDFS in patients with stage T1c, T2a, T2b, T2c and T3 groups at 5 years was 74%, 79%, 72%, 24% and 33%, respectively ($P < 0.0001$). The BDFS in patients in the low-, intermediate- and high-risk groups at 5 years was 84%, 64% and 45%, respectively ($P < 0.0001$). The BDFS in patients treated with or without neoadjuvant hormonal therapy at 7 years was 73% and 53% ($P < 0.0001$), respectively. Postoperative erectile dysfunction was noted in 33 out of 114 (28.9%) patients who were preoperatively potent.

In a recent retrospective study, 137 patients with PCa underwent HIFU (24). After a median follow-up of 36 months, 22% of the patients relapsed according to the Phoenix criteria. The 5-year DFS rate was 78% based on these criteria, and 91%, 81% and 62% in the low-, intermediate- and high-risk group, respectively. Urge incontinence (16 cases) and dysuria (33 cases) occurred after removal of the urethral catheter in 11.8% and 24.1%, respectively.

To evaluate whether the location (apex/midgland/base) of PCa influences the risk of incomplete transrectal HIFU ablation, Bouiter *et al*. (25) analysed 99 patients who underwent PCa HIFU ablation (Ablatherm; EDAP, Vaulx-en-Velin, France) with a 6-mm safety margin at the apex, and had systematic biopsies at 3-6 months after treatment. After treatment, residual cancer was found in 36 patients (36.4%) and 50 sextants (8.4%); 30 (60%) positive sextants were in the apex, 12 (24%) in the midgland, and eight (16%) in the base. Statistical analysis showed that the mean (95% CI) probability for a sextant to remain positive after HIFU ablation was 8.8% (3.5-20.3%) in the base, 12.7% (5.8-25.9%) in the midgland, and 41.7% (27.2-57.89%) in the apex. When a 6-mm apical safety margin was used, treatment-associated side effects, especially incontinence and erectile dysfunction, were fewer but residual cancer after HIFU ablation was significantly more frequent in the apex.

Komura *et al*. (26) have analysed the oncological outcome in 144 patients with T1/T2 PCa and a median follow-up of 47 (2-70) months. Thirty-nine percent patients relapsed and approximately 40% developed a clinical or subclinical urethral stricture postoperatively. Most interestingly, the 5-year DFS was significantly better in those with a stricture as compared to those without (78.2% vs. 47.8%, $P < 0.001$), indicating the need for more aggressive treatment especially at the apex of the prostate.

11.3.2 ***Complications of HIFU***

Urinary retention appears to be one of the most common side effects of HIFU, developing in almost all patients, with the mean interval of catheterisation via a suprapubic tube varying between 12 and 35 days (16-18). Grade I and II urinary stress incontinence occurs in about 12% of patients. Subsequent TURP or bladder neck incision to treat subvesical obstruction is common, and is sometimes even performed at the time of HIFU. Post-operative impotence occurs in 55-70% of patients.

Elterman *et al*. (27) have treated 95 patients with clinically organ-confined PCa using the Sonablate-500 device, and have evaluated the type and frequency of treatment-associated complications. With a minimum follow-up of 6 months, 17% (7/41) of the men had significant incontinence and 2% developed significant erectile dysfunction. Early and late subvesical obstruction necessitating surgical treatment occurred in 17 (17.9%) and 20 (21.1%) patients, respectively.

11.4 Focal therapy of PCa

During the past two decades, there has been a trend towards earlier diagnosis of PCa due to greater public and professional awareness, leading to the adoption of both formal and informal screening strategies. The effect of this has been to identify men with smaller tumours at an earlier stage, which occupy only 5-10% of the prostate volume, with a greater propensity for unifocal or unilateral disease (28-30).

Most focal therapies to date have been achieved with ablative technologies; cryotherapy, HIFU or photodynamic therapy. So far, three groups have proposed that non-diseased prostate tissue be left untreated in the hope and expectation that genitourinary function might be preserved and the tumour treated adequately (31-33). Although focal therapy is currently not the standard for men with organ-confined PCa, it is the therapeutic approach with the most important future potential.

11.4.1 ***Pre-therapeutic assessment of patients***

The high number of random and systematic errors associated with TRUS-guided biopsy regimens means that this procedure is not sufficiently accurate for selecting candidates for focal therapy. The current standard for characterising men considering focal therapy is transperineal prostate biopsy using a template-guided approach (34,35). When used with a 5-mm sampling frame, this approach can rule in and rule out PCa foci of 0.5 and 0.2 mL volume, with 90% certainty (36). Thus, the exact anatomical localisation of the index lesion - defined as the biologically most aggressive - can be accurately determined.

11.4.2 ***Patient selection for focal therapy***

The primary objective of treatment must be the eradication of measurable and biologically aggressive disease. However, although treatment is usually intended to be one-off, patients should know that further treatment might be necessary in the future.

Based on published data, the following criteria identify possible candidates for currently ongoing trials of focal treatment:

- Candidates for focal therapy should ideally undergo transperineal template mapping biopsies. However, a state-of-the-art multifunctional MRI with TRUS biopsy at expert centres may be acceptable.
- Focal therapy should be limited to patients with a low to moderate risk. The clinical stage of the tumour should be < cT2a and the radiological stage < cT2b.
- Patients with previous prostate surgery should be counselled with caution because no data on

functional and oncological outcomes are available. Patients who have undergone radiation therapy of the prostate are not candidates for focal therapy.

- Patients must be informed that the therapy is still experimental and that there is a possibility of repeat-treatment.

11.5 Summary of experimental therapeutic options to treat clinically localised PCa

Conclusion	LE
All other minimally invasive treatment options - such as HIFU microwave and electrosurgery - are still experimental or investigational. For all of these procedures, a longer follow-up is mandatory to assess their true role in the management of PCa.	

Recommendation	GR
In patients who are unfit for surgery, or with a life expectancy < 10 years CSAP has evolved from an investigational therapy to a possible alternative treatment for PCa.	C
Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	C

11.6 References

1. Fahmy WE, Bissada NK. Cyrosurgery for prostate cancer. Arch Androl 2003 Sep-Oct;49(5):397-407. http://www.ncbi.nlm.nih.gov/pubmed/12893518
2. Rees J, Patel B, Macdonagh R, et al. Cryosurgery for prostate cancer. BJU Int 2004 Apr;93(6):710-4. http://www.ncbi.nlm.nih.gov/pubmed/15049977
3. Han KR, Belldegrun AS. Third-generation cryosurgery for primary and recurrent prostate cancer. BJU Int 2004 Jan;93(1):14-8. http://www.ncbi.nlm.nih.gov/pubmed/14678360
4. Beerlage HP, Thüroff S, Madersbacher S, et al. Current status of minimally invasive treatment options for localized prostate carcinoma. Eur Urol 2000 Jan;37(1):2-13. http://www.ncbi.nlm.nih.gov/pubmed/10671777
5. Hull GW, Rabbani F, Abbas F, et al. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol 2002 Feb;167(2Pt1):528-34. http://www.ncbi.nlm.nih.gov/pubmed/11792912
6. Long JP, Bahn D, Lee F, et al. Five-year retrospective, multi-institutional pooled analysis of cancer-related outcomes after cryosurgical ablation of the prostate. Urology 2001 Mar;57(3):518-23. http://www.ncbi.nlm.nih.gov/pubmed/11248631
7. Donelly BJ, Saliken JC, Ernst DS, et al. Prospective trial of cryosurgical ablation of the prostate: five year results. Urology 2002 Oct;60(4):645-9. http://www.ncbi.nlm.nih.gov/pubmed/12385926
8. Han K, Cohen J, Miller R, et al. Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicentre experience. J Urol 2003 Oct;170(4Pt1):1126-30. http://www.ncbi.nlm.nih.gov/pubmed/14501706
9. Bahn DK, Lee F, Baldalament R, et al. Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. Urology 2002 Aug;60(2 Suppl 1):3-11. http://www.ncbi.nlm.nih.gov/pubmed/12206842
10. Koppie TM, Shinohara K, Grossfeld GD, et al. The efficacy of cryosurgical ablation of prostate cancer: the University of California, San Francisco experience. J Urol 1999 Aug;162(2):427-32. http://www.ncbi.nlm.nih.gov/pubmed/10411051
11. De La Taille A, Benson MC, Bagiella E, et al. Cryoablation for clinically localized prostate cancer using an argon-based system: complication rates and biochemical recurrence. BJU Int 2000 Feb;85(3): 281-6. http://www.ncbi.nlm.nih.gov/pubmed/10671882
12. Aus G. Current status of HIFU and cryotherapy in prostate cancer-a review. Eur Urol 2006 Nov;50(5):927-34. http://www.ncbi.nlm.nih.gov/pubmed/16971038
13. Onik G, Narayan P, Vaughan D, et al. Focal 'nerve-sparing' cryosurgery for treatment of primary prostate cancer: a new approach to preserving potency. Urology 2002 Jul;60(1):109-14. http://www.ncbi.nlm.nih.gov/pubmed/12100934

14. Robinson JW, Donnelly BJ, Saliken JC, et al. Quality of life and sexuality of men with prostate cancer 3 years after cryosurgery. Urology 2002 Aug;60(2 Suppl 1):12-8.
http://www.ncbi.nlm.nih.gov/pubmed/12206843
15. Robinson JW, Donnelly BJ, Siever JE, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. Cancer 2009 Oct;115(20):4695-704.
http://www.ncbi.nlm.nih.gov/pubmed/19691092
16. Madersbacher S, Marberger M. High-energy shockwaves and extracorporeal high-intensity focused ultrasound. J Endourol 2003 Oct;17(8):667-72.
http://www.ncbi.nlm.nih.gov/pubmed/14622487
17. Poissonnier L, Chapelon JY, Rouviere O, et al. Control of prostate cancer by transrectal HIFU in 227 patients. Eur Urol 2007 Feb;51(2):381-7.
http://www.ncbi.nlm.nih.gov/pubmed/16857310
18. Gelet A, Chapelon JY, Bouvier R, et al. Local control of prostate cancer by transrectal high intensity focused ultrasound therapy: preliminary results. J Urol 1999 Jan;161(1):156-62.
http://www.ncbi.nlm.nih.gov/pubmed/10037389
19. Thüroff S, Chaussy C, Vallancien G, et al. High-intensity focused ultrasound and localized prostate cancer: efficacy results from the European multicentric study. J Endourol 2003 Oct;17(8):673-7.
http://www.ncbi.nlm.nih.gov/pubmed/14622488
20. Blana A, Walter B, Rogenhofer S, et al. High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-year experience. Urology 2004 Feb;63(2)297-300.
http://www.ncbi.nlm.nih.gov/pubmed/14972475
21. Uchida T, Illing RO, Cathcart PJ, et al. To what extent does the prostate-specific antigen nadir predict subsequent treatment failure after transrectal high-intensity focused ultrasound therapy for presumed localized adenocarcinoma of the prostate? BJU Int 2006 Sep;98(3):537-9.
http://www.ncbi.nlm.nih.gov/pubmed/16925749
22. Blana A, Rogenhofer S, Ganzer R, et al. Eight years'experience with high-intensity focused ultrasonography for treatment of localized prostate cancer. Urology 2008 Dec;72(6):1329-33.
http://www.ncbi.nlm.nih.gov/pubmed/18829078
23. Uchida T, Shoji S, Nakano M, et al. Transrectal high-intensity focused ultrasound for the treatment of localized prostate cancer: eight-year experience. Int J Urol 2009 Nov;16(11):881-6.
http://www.ncbi.nlm.nih.gov/pubmed/19863624
24. Inoue Y, Goto K, Hayashi T, et al. Transrectal high-intensity focused ultrasound for treatment of localized prostate cancer. Int J Urol 2011 May;18(5):358-62.
http://www.ncbi.nlm.nih.gov/pubmed/21449970
25. Boutier R, Girouin N, Cheikh AB, et al. Location of residual cancer after transrectal high-intensity focused ultrasound ablation for clinically localized prostate cancer. BJU Int 2011 Dec;108(11):1776-81.
http://www.ncbi.nlm.nih.gov/pubmed/21711432
26. Komura K, Inamoto T, Black PC, et al. Clinically significant urethral stricture and/or subclinical urethral stricture after high-intensity focused ultrasound correlates with disease-free survival in patients with localized prostate cancer. Urol Int 2011;87(3):276-81.
http://www.ncbi.nlm.nih.gov/pubmed/21912100
27. Elterman DS, Barkin J, Radomski SB, et al. Results of high intensity focused ultrasound treatment of prostate cancer: early Canadian experience at a single center. Can J Urol 2011 Dec;18(6):6037-42.
http://www.ncbi.nlm.nih.gov/pubmed/22166332
28. Mouraviev V, Mayes JM, Polascik TJ. Pathologic basis of focal therapy for early-stage prostate cancer. Nat Rev Urol 2009 Apr;6(4):205-15.
http://www.ncbi.nlm.nih.gov/pubmed/19352395
29. Cooperberg MR, Broering JM, Kantoff PW, et al. Contemporary trends in low risk prostate cancer: risk assessment and treatment. J Urol 2007 Sep;178(3Pt 2):S14-9.
http://www.ncbi.nlm.nih.gov/pubmed/17644125
30. Polascik TJ, Mayes JM, Sun L, et al. Pathologic stage T2a and T2b prostate cancer in the recent prostate-specific antigen era: implications for unilateral ablative therapy. Prostate 2008 Sep;68(13):1380-6.
http://www.ncbi.nlm.nih.gov/pubmed/18543281
31. Ahmed HU, Pendse D, Illing R, et al. Will focal therapy become standard of care for men with localized prostate cancer? Nat Clin Pract Oncol 2007 Nov;4(11):632-42.
http://www.ncbi.nlm.nih.gov/pubmed/17965641

32. Eggener SE, Scardino PT, Carroll PR, et al. International Task Force on Prostate Cancer and the Focal Lesion Paradigm. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. J Urol 2007 Dec;178(6):2260-7. http://www.ncbi.nlm.nih.gov/pubmed/17936815
33. Crawford ED, Barqawi A. Targeted focal therapy: a minimally invasive ablation technique for early prostate cancer. Oncology (Williston Park) 2007 Jan;21(1):27-32. http://www.ncbi.nlm.nih.gov/pubmed/17313155
34. Onik G, Miessau M, Bostwick DG. Three-dimensional prostate mapping biopsy has a potentially significant impact on prostate cancer management. J Clin Oncol 2009 Sep;10:27(26):4321-6. http://www.ncbi.nlm.nih.gov/pubmed/19652073
35. Onik G, Barzell W. Transperineal 3D mapping biopsy of the prostate: an essential tool in selecting patients for focal prostate cancer therapy. Urol Oncol 2008 Sep-Oct;26(5):506-10. http://www.ncbi.nlm.nih.gov/pubmed/18774464
36. Crawford ED, Wilson SS, Torkko KC, et al. Clinical staging of prostate cancer: a computer-simulated study of transperineal prostate biopsy. BJU Int 2005 Nov;96(7):999-1004. http://www.ncbi.nlm.nih.gov/pubmed/16225516

12. HORMONAL THERAPY; RATIONALE AND AVAILABLE DRUGS

12.1 Introduction

In 1941, Huggins and Hodges assessed the effect of surgical castration and oestrogen administration on the progression of metastatic prostate cancer (PCa). They demonstrated for the first time the responsiveness of PCa to androgen deprivation (1,2). Since then, androgen-suppressing strategies have become the mainstay of management of advanced PCa. More recently, there has been a move towards the increasing use of hormonal treatment in younger men with earlier disease (i.e. non-metastatic) or recurrent disease after definitive treatment, either as the primary single-agent therapy or as a part of a multimodality approach (3).

However, even if hormonal treatment effectively palliates the symptoms of advanced disease, there is currently no conclusive evidence to show that it extends life.

*12.1.1 **Basics of hormonal control of the prostate***

Prostate cells are physiologically dependent on androgens to stimulate growth, function and proliferation. Testosterone, although not tumorigenic, is essential for the growth and perpetuation of tumour cells (4). The testes are the source of most androgens, with adrenal biosynthesis providing only 5-10% of androgens (i.e. androstenedione, dihydroepiandrosterone and dihydroepiandrosterone sulphate).

Testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis. Hypothalamic luteinising hormone-releasing hormone (LHRH) stimulates the anterior pituitary gland to release luteinising hormone (LH) and follicle-stimulating hormone (FSH). Luteinising hormone stimulates the Leydig cells of the testes to secrete testosterone. Within the prostate cell, testosterone is converted to 5-α-dihydrotestosterone (DHT) by the enzyme 5-α-reductase; DHT is an androgenic stimulant about 10 times more powerful than testosterone. Meanwhile, circulating testosterone is peripherally aromatised and converted to oestrogens, which together with circulating androgens, exert a negative feedback control on hypothalamic LH secretion.

If prostate cells are deprived of androgenic stimulation, they undergo apoptosis (programmed cell death). Any treatment that results ultimately in suppression of androgen activity is referred to as androgen deprivation therapy (ADT).

*12.1.2 **Different types of hormonal therapy***

Androgen deprivation can be achieved by either suppressing the secretion of testicular androgens by surgical or medical castration or inhibiting the action of circulating androgens at the level of their receptor in prostate cells using competing compounds known as anti-androgens. In addition, these two methods of androgen deprivation can be combined to achieve what is commonly known as complete (or maximal or total) androgen blockade (CAB).

12.2 Testosterone-lowering therapy (castration)

*12.2.1 **Castration level***

Surgical castration is still considered the ‘gold standard’ for ADT, against which all other treatments are

rated. Removal of the testicular source of androgens leads to a considerable decline in testosterone levels and induces a hypogonadal status, although a very low level of testosterone (known as the 'castration level') persists.

The standard castrate level is < 50 ng/dL. It was defined more than 40 years ago, when testosterone level testing was limited. However, current testing methods using chemiluminescence have found that the mean value of testosterone after surgical castration is 15 ng/dL(1.7 nmol/L) (5). This has led to a revisiting of the current definition of castration, with many authors suggesting a more appropriate level is < 20 ng/dL (0.1 nmol/L).

*12.2.2 **Bilateral orchiectomy***

Bilateral orchiectomy, which is either total or subcapsular (i.e. with preservation of tunica albuginea and epididymis), is a simple and virtually complication-free surgical procedure. It is easily performed under local anaesthesia (6) and is the quickest way to achieve a castration level, usually within less than 12 hours.

The main drawback of orchiectomy is that it may have a negative psychological effect: some men consider it to be an unacceptable assault on their manhood. In addition, it is irreversible and does not allow for intermittent treatment.

12.3 Oestrogens

Oestrogens have several mechanisms of action:

- down-regulation of LHRH secretion;
- androgen inactivation;
- direct suppression of Leydig cell function;
- direct cytotoxicity to the prostate epithelium (in-vitro evidence only) (7).

*12.3.1 **Diethylstilboesterol (DES)***

Diesthylstilboesterol (DES) is the most commonly used oestrogen in PCa. Early studies by the Veterans Administration Co-operative Urological Research Group (VACURG) tested oral DES at a dosage of 5 mg/ day. However, this dosage was associated with high cardiovascular morbidity and mortality, due to first-pass hepatic metabolism and formation of thrombogenic metabolites. Lower oral doses of 1 mg/day and 3 mg/ day were therefore tested and were both found to provide a therapeutic efficacy similar to that of bilateral orchiectomy. However, 3 mg daily of DES was still associated with high cardiotoxicity. Although 1 mg daily of DES resulted in much fewer adverse cardiovascular events than 5 mg daily of DES, the side-effects were still significantly greater than with castration. Recently, there has been renewed interest in using oestrogens (8).

*12.3.2 **Renewed interest in oestrogens***

There are three main reasons for a renewed interest in using oestrogens to treat PCa:

1. Oestrogens suppress testosterone levels and do not seem to lead to bone loss and cognitive decline (9) as do LHRH agonists (LE: 3).
2. In phase II trials for castration refractory PCa (CRPC), oestrogenic compounds (DES, DES-diphosphate) have induced prostate-specific antigen (PSA) response rates as high as 86%.
3. Discovery of a new oestrogen receptor-®(ER-®), possibly involved in prostate tumorigenesis (7).

*12.3.3 **Strategies to counteract the cardiotoxicity of oestrogen therapy***

Two strategies have been used to try and neutralise the cardiotoxicity associated with oestrogen therapy, which is its main disadvantage:

- parenteral route of administration - so avoiding first-pass hepatic metabolism;
- concomitant use of cardiovascular-protective agents.

The Scandinavian Prostatic Cancer Group Study 5 is a large prospective randomized trial which compared a parenteral oestrogen (polyoestradiol phosphate) with CAB (orchiectomy, or an LHRH agonist + flutamide). No difference was observed in disease or overall survival between the treatment groups nor was there any increase in cardiovascular mortality. However, in the oestrogen-treated group, there was a significantly higher incidence of non-fatal adverse cardiovascular events, particularly ischaemic and heart decompensation events (10).

In addition, thromboembolic complications have been observed in trials evaluating the combination of DES, 1 mg/day or 3 mg/ day, with either a low dose of warfarin sodium, 1 mg/day, or a low dose of aspirin, 75-100 mg/day, for the prevention of cardiovascular toxicity (11,12).

*12.3.4 **Conclusions***

Diethylstilboesterol is an effective form of hormonal therapy comparable to that of bilateral orchiectomy (8) (LE:1a). However, there is still concern about the significant cardiovascular side-effects of DES, even at lower

dosages. Further data are needed before oestrogens can be re-admitted into clinical practice as a standard first-line treatment option.

12.4 LHRH agonists

Long-acting LHRH agonists have been used in advanced PCa for more than 15 years and are currently the main forms of ADT (3). They are synthetic analogues of LHRH, generally delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. After the first injection, they stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH release leading to the 'testosterone surge' or 'flare-up' phenomenon, which begins 2-3 days later and lasts for about 1 week. No significant difference in efficacy has been observed between the different drugs. But the different drugs have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection. It is important to carefully follow the directions for using a particular drug to avoid any misuse.

*12.4.1 **Achievement of castration levels***

Chronic exposure to LHRH agonists eventually results in down-regulation of LHRH-receptors, suppressing pituitary LH and FSH secretion and testosterone production. Testosterone levels decrease to castration levels usually within 2-4 weeks (13). However, about 10% of patients treated with LHRH agonists fail to achieve castration levels (14). This proportion rises to 15% if the castration threshold is defined as 20 ng/dL.

A recent meta-analysis evaluating single-therapy ADT for advanced PCa suggested that LHRH agonists have a similar efficacy compared to orchiectomy or DES (8) (LE: 1a) when 2-year survival was the target outcome. This finding raises the question about the clinical impact of changing the definition of the castrate testosterone level from 50 ng/dL to 20 ng/dL. In addition, although only based on indirect comparison, the LHRH agonists seemed equally effective whatever their formulation (8) (LE: 3).

*12.4.2 **Flare-up phenomenon***

Today, LHRH agonists have become the 'standard of care' in hormonal therapy. The main concerns are the potentially detrimental effects associated with 'flare phenomenon' in advanced disease, namely increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and fatal cardiovascular events due to hypercoagulation status.

A recent review (15) concluded that clinical flare needs to be distinguished from the more common biochemical flare (i.e. increasing levels of PSA), and even from asymptomatic radiographic evidence of progression. Patients at risk are usually patients with high-volume, symptomatic, bony disease, which account for only 4-10% of M1 patients. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare, but does not completely suppress the risk. Anti-androgens should be started on the same day as the LHRH analogue and should be continued for a 2-week period. The overall clinical impact of this initial flare is unknown.

Some mini-flares have also been observed with the long-term use of LHRH agonists. The clinical impact is unknown but it has been suggested a mini-flare is associated with a negative impact on overall survival (*see Section 15*).

12.5 LHRH antagonists

In contrast to LHRH agonists, LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a rapid decrease in LH, FSH and testosterone levels without any flare. This seemed to be a more desirable mechanism of action and has made LHRH antagonists very attractive to use. However, practical shortcomings have limited clinical studies, as many LHRH antagonists have been associated with serious and life-threatening histamine-mediated side-effects and, until recently, no depot formulation was available.

*12.5.1 **Abarelix***

Two published phase III trials compared abarelix, with an LHRH agonist, (16), and with CAB (17), in patients with metastatic or recurrent PCa. Both trials showed no difference in achieving and maintaining castration levels of testosterone and in reducing serum PSA, without any biochemical 'flare up' phenomenon in the abarelix arm. Data on survival end-points and long-term safety are not yet available.

The US Food and Drug Administration have recently licensed the clinical use of abarelix in metastatic and symptomatic PCa, for which no other treatment option is available. However, based on prolonged analysis, the FDA has issued a warning about allergic reactions with the long-term use of abarelix, which has resulted in suspension of its further development.

12.5.2 ***Degarelix***

Degarelix is another LHRH antagonist in a monthly subcutaneous formulation. Based on a large, randomized, non-inferiority, dose-finding study (n = 610) the standard dosage of degarelix should be 240 mg the first month, followed by 80 mg monthly injections. More than 95% of patients achieved a castrate level at day 3, which was associated with a quick decline in PSA (as early as day 14). No allergic reaction was observed. The main specific side-effect of degarelix was a painful injection (moderate or mild) reported in 40% of patients, mainly after the first injection. An extended follow-up has been recently published (median 27.5 months), suggesting that degarelix might result in better progression-free survival compared to monthly leuprorelin (18).

12.5.3 ***Conclusions***

Overall, this new family of agents seems appealing, but their advantages over LHRH agonists are far from proven. The use of LHRH antagonists is limited by a monthly formulation. Suppression of the initial flare-up with monotherapy is only clinically relevant in a few, symptomatic, metastatic patients.

12.6 Anti-androgens

These oral compounds are classified according to their chemical structure as:

- steroidal, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate;
- non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide.

Both classes compete with androgens at the receptor level. This is the sole action of non-steroidal anti-androgens. In addition, steroidal anti-androgens have progestational properties leading to a central inhibition. As a consequence, non-steroidal antiandrogens do not lower testosterone levels, which remain normal or, conversely, slightly elevated.

12.6.1 ***Steroidal anti-androgens***

These compounds are synthetic derivatives of hydroxyprogesterone. Since steroidal antiandrogens lower testosterone levels, the main pharmacological side-effects are loss of libido and erectile dysfunction, while gynaecomastia is quite rare. The non-pharmacological side-effects are cardiovascular toxicity (4-40% for CPA) and hepatotoxicity.

12.6.1.1 Cyproterone acetate (CPA)

Cyproterone acetate was the first anti-androgen to be licensed and is the most widely used. However, it is the least studied.

The most effective dose of CPA in monotherapy is still unknown. Although CPA has a relatively long half-life (31-41 hours), it is usually administered in two or three fractionated doses of 100 mg each (19). There has been only one randomized trial (20) comparing CPA with standard medical castration, suggesting a poorer OS compared to LHRH analogs. Although there are other studies in CPA monotherapy, methodological limitations prevent firm conclusions being made from their results about the relative efficacy of CPA and castration.
The only comparative study on anti-androgens as monotherapy was recently published by the EORTC, comparing CPA to flutamide in metastatic PCa. No difference in cancer-specific survival and OS at a median follow-up of 8.6 years was observed, although the study was underpowered (21) (LE: 1b).

12.6.1.2 Megestrol acetate and medroxyprogesterone acetate

Very limited information is available on these two compounds. But the overall poor efficacy (22) has prevented them from being recommended for either primary- or second-line hormonal therapy.

12.6.2 ***Non-steroidal anti-androgens***

The use of non-steroidal anti-androgens as monotherapy has been promoted on the basis of improved quality of life (QoL) and compliance compared to castration. They do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are preserved (23). Although they have not been directly compared in a monotherapy setting, the severity of pharmacological side-effects, namely gynaecomastia, breast pain and hot flashes, appears similar for the three available non-steroidal anti-androgens. However, there are differences in non-pharmacological side-effects, with bicalutamide showing a more favourable safety and tolerability profile than nilutamide and flutamide (24). All three agents share a common liver toxicity and liver enzymes must be monitored regularly.

12.6.2.1 Nilutamide

There are no comparative trials of nilutamide monotherapy with castration or with other anti-androgens. Non-pharmacological side-effects are visual disturbances (i.e. delayed adaptation to darkness), alcohol intolerance, nausea, hepatotoxicity, and interstitial pneumonitis. Even if exceptional, interstitial pneumonitis is potentially

life-threatening and is specific to nilutamide. Nilutamide is not licensed for monotherapy.

12.6.2.2 Flutamide
Flutamide was the first non-steroidal anti-androgen available for clinical use. Although it has been studied as monotherapy for more than 20 years, there are no dose-finding studies against a currently accepted end-point (e.g. PSA response). Flutamide is a pro-drug, and the half-life of the active metabolite is 5-6 hours, so it must be administered three times daily. The recommended daily dosage is 750 mg (19). The non-pharmacological side-effects of flutamide are diarrhoea and hepatotoxicity (occasionally fatal).

12.6.2.3 Bicalutamide
Dose-finding studies of bicalutamide
The dosage licensed for use in CAB is 50 mg/day, and 150 mg dosage for monotherapy. The non-pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%), which may be prevented by anti-oestrogens (25-27), prophylactic radiotherapy (28), or treatment with surgical mastectomy or radiotherapy (29). However, bicalutamide clearly offers bone protection compared with LHRH analogues and probably LHRH antagonists (30,31).

12.7 New compounds

Our knowledge of castration resistant prostate cancer (CRPC) remains incomplete, but is starting to become clearer (5,6). It is thought that castrate resistant disease is mediated through two main overlapping mechanisms, which are androgen-receptor (AR)-independent and AR-dependent (see chapter . . .). This has led to the development of two new major compounds targeting the androgen axis: abiraterone acetate and lenzalutamide.

12.7.1 ***Abiraterone acetate***
Abiraterone acetate is a CYP17 inhibitor. It represents an improvement of ketoconazole, which is no longer used or available. By blocking CYP17, abiraterone acetate significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level as inside the cancer cells (intracrine mechanism). In castrate resistant prostate cells, the intracellular androgen level is increased compared to androgen sensitive cells, suggesting an adaptive mechanism, through an increase of androgen biosynthesis (32) enzymes.

12.7.2 ***Lenzalutamide***
Lenzalutamide (previously known as MDV 3100) is a novel anti-androgen with a higher affinity compared to bicalutamide. It blocks the transfer of ARs to the nucleus so that no agonist-like activity should ever occur. In contrast, currently available drugs still permit the transfer of ARs to the nucleus. The ability of lenzalutamide to block AR transfer is important because over-expression of the AR has been observed in CRPC.

Both drugs have been developed for use in CRPC after docetaxel has been used. Abiraterone acetate and Lenzalutamide have shown a significant overall improvement in survival (33,34). Detailed results of both drugs are presented in chapter 20. Both drugs represent an outstanding opportunity for the future treatment of CRPC and confirm that the CRPC status is far from being a hormonal-resistant status.

12.8 References

1. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. J Urol 2002 Feb;167(2P 2):948-51; discussion 952.
   http://www.ncbi.nlm.nih.gov/pubmed/11905923
2. Huggins C, Stevens RE Jr, Hodges CV. Studies on prostate cancer. II. The effect of castration on advanced carcinoma of the prostate gland. Arch Surg 1941;43:209-23.
3. McLeod DG. Hormonal therapy: historical perspective to future directions. Urology 2003 Feb;61(2 Suppl 1):3-7.
   http://www.ncbi.nlm.nih.gov/pubmed/12667881
4. Walsh PC. Physiologic basis for hormonal therapy in carcinoma of the prostate. Urol Clin North Am 1975 Feb;2(1):125-40.
   http://www.ncbi.nlm.nih.gov/pubmed/48206
5. Oefelein MG, Feng A, Scolieri MJ, et al. Reassessment of the definition of castrate levels of testosterone: implications for clinical decision making. Urology 2000 Dec;56(6):1021-4.
   http://www.ncbi.nlm.nih.gov/pubmed/11113751

6. Desmond AD, Arnold AJ, Hastie KJ. Subcapsular orchiectomy under local anaesthesia. Technique, results and implications. Br J Urol 1988 Feb;61(2):143-5.
http://www.ncbi.nlm.nih.gov/pubmed/3349279
7. Limonta P, Montagnani MM, Moretti RM. LHRH analogues as anticancer agents: pituitary and extrapituitary sites of action. Expert Opin Investig Drugs 2001 Apr;10(4):709-20.
http://www.ncbi.nlm.nih.gov/pubmed/11281820
8. Morote J, Orsola A, Planas J, et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. J Urol 2007 Oct;178(4 Pt 1): 1290-5.
http://www.ncbi.nlm.nih.gov/pubmed/17698136
9. Seidenfeld J, Samson DJ, Hasselblad V, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. Ann Intern Med 2000 Apr;132(7):566-77.
http://www.ncbi.nlm.nih.gov/pubmed/10744594
10. Bubley GJ. Is the flare phenomenon clinically significant? Urology 2001 Aug;58(2 Suppl 1):5-9.
http://www.ncbi.nlm.nih.gov/pubmed/11502435
11. McLeod DG, Zinner N, Tomera K, et al. A phase 3, multicentre, open-label, randomized study of abarelix versus leuprolide acetate in men with prostate cancer. Urology 2001 Nov;58(5):756-61.
http://www.ncbi.nlm.nih.gov/pubmed/11711355
12. Trachtenberg J, Gittleman M, Steidle C, et al. A phase 3, multicentre, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. J Urol 2002 Apr;167(4):1670-4.
http://www.ncbi.nlm.nih.gov/pubmed/11912385
13. Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int 2008 Dec;102(11):1531-8.
http://www.ncbi.nlm.nih.gov/pubmed/19035858
14. Crawford ED, Tombal B, Miller K, et al. A phase III extension trial with a 1-arm crossover from leuprolide to degarelix: comparison of gonadotropin-releasing hormone agonist and antagonist effect on prostate cancer. J Urol 2011 Sep;186(3):889-97.
http://www.ncbi.nlm.nih.gov/pubmed/21788033
15. Oh WK. The evolving role of estrogen therapy in prostate cancer. Clin Prostate Cancer 2002 Sep;1(2):81-9.
http://www.ncbi.nlm.nih.gov/pubmed/15046698
16. Scherr DS, Pitts WR Jr. The non-steroidal effects of diethylstilbestrol: the rationale for androgen deprivation therapy without estrogen deprivation in the treatment of prostate cancer. J Urol 2003 Nov;170(5):1703-8.
http://www.ncbi.nlm.nih.gov/pubmed/14532759
17. Hedlund PO, Johansson R, Damber JE, et al. SPCG-5 STUDY GROUP. Significance of pretreatment cardiovascular morbidity as a risk factor during treatment with parenteral oestrogen or combined androgen deprivation of 915 patients with metastasized prostate cancer: evaluation of cardiovascular events in a randomized trial. Scand J Urol Nephrol 2011 Nov;45(5):346-53.
http://www.ncbi.nlm.nih.gov/pubmed/21627403
18. Farrugia D, Ansell W, Singh M, et al. Stilboestrol plus adrenal suppression as salvage treatment for patients failing treatment with luteinizing hormone-releasing hormone analogues and orchidectomy. BJU Int 2000 Jun;85(9):1069-73.
http://www.ncbi.nlm.nih.gov/pubmed/10848697
19. Mahler C, Verhelst J, Denis L. Clinical pharmacokinetics of the antiandrogens and their efficacy in prostate cancer. Clin Pharmacokinet 1998 May;34(5):405-17.
http://www.ncbi.nlm.nih.gov/pubmed/9592622
20. Moffat LE. Comparison of Zoladex, diethylstilboestrol and cyproterone acetate treatment in advanced prostate cancer. Eur Urol 1990;18(Suppl 3):26-7.
http://www.ncbi.nlm.nih.gov/pubmed/2151272
21. Schroder FH, Whelan P, de Reijke TM, et al. Metastatic prostate cancer treated by flutamide versus cyproterone acetate. Final analysis of the 'European Organization for Research and Treatment of Cancer' (EORTC) Protocol 30892. Eur Urol 2004 Apr;45(4):457-64.
http://www.ncbi.nlm.nih.gov/pubmed/15041109

22. Pavone-Macaluso M, Schröder FH, de Voogt HJ, et al. EORTC protocol 30761: a randomized study of non-metastatic and metastatic prostatic cancer treated by cyproterone acetate versus diethylstilbestrol and medroxyprogesterone acetate. European Organization for Research on Treatment of Cancer Urological Group. Prog Clin Biol Res 1989;303:111-6. http://www.ncbi.nlm.nih.gov/pubmed/2528735
23. Iversen P. Antiandrogen monotherapy: indications and results. Urology 2002;60(3 Suppl 1):64-71. http://www.ncbi.nlm.nih.gov/pubmed/12231053
24. McLeod DG. Tolerability of non-steroidal antiandrogens in the treatment of advanced prostate cancer. Oncologist 1997;2(1):18-27. http://www.ncbi.nlm.nih.gov/pubmed/10388026
25. Boccardo F, Rubagotti A, Battaglia M, et al. Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. J Clin Oncol 2005 Feb;23(4):808-15. http://www.ncbi.nlm.nih.gov/pubmed/15681525
26. Fradet Y, Egerdie B, Andersen M, et al. Tamoxifen as prophylaxis for prevention of gynaecomastia and breast pain associated with bicalutamide 150 mg monotherapy in patients with prostate cancer: a randomised, placebo-controlled, dose-response study. Eur Urol 2007 Jul;52(1):106-14. http://www.ncbi.nlm.nih.gov/pubmed/17270340
27. Bedognetti D, Rubagotti A, Conti G, et al. An open, randomised, multicentre, phase 3 trial comparing the efficacy of two tamoxifen schedules in preventing gynaecomastia induced by bicalutamide monotherapy in prostate cancer patients. Eur Urol 2010 Feb;57(2):238-45. http://www.ncbi.nlm.nih.gov/pubmed/19481335
28. Dicker AP. The safety and tolerability of low-dose irradiation for the management of gynaecomastia caused by antiandrogen monotherapy. Lancet Oncol 2003 Jan;4(1):30-6. http://www.ncbi.nlm.nih.gov/pubmed/12517537
29. Van Poppel H, Tyrrell CJ, Haustermans K, et al. Efficacy and tolerability of radiotherapy as treatment for bicalutamide-induced gynaecomastia and breast pain in prostate cancer. Eur Urol 2005 May;47(5):587-92. http://www.ncbi.nlm.nih.gov/pubmed/15826748
30. Smith MR, Goode M, Zietman AL, et al. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Oncol 2004 Jul;22(13):2546-53. http://www.ncbi.nlm.nih.gov/pubmed/15226323
31. Wadhwa VK, Weston R, Mistry R, et al. Long-term changes in bone mineral density and predicted fracture risk in patients receiving androgen-deprivation therapy for prostate cancer, with stratification of treatment based on presenting values. BJU Int 2009 Sep;104(6):800-5. http://www.ncbi.nlm.nih.gov/pubmed/19338564
32. Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of Intratumoral Androgens in Metastatic Prostate Cancer: A Mechanism for Castration-Resistant Tumor Growth. Cancer Res 2008 Jun; 68(11):4447-4454. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2536685/
33. De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011 May; 364(21):1996-2005. http://www.ncbi.nlm.nih.gov/pubmed/21612468
34. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012 May; 367(13):1187-97. http://www.ncbi.nlm.nih.gov/pubmed/22894553

13. METASTATIC PROSTATE CANCER - HORMONAL THERAPY

13.1 Prognostic factors

The M1 population is heterogeneous (Table 18). Various prognostic factors have been suggested, including general prognostic factors, such as pain, ECOG score, Gleason score or biological information (haemoglobin level, CRP level, alkaline phosphatase), which still need to be confirmed in large trials. The most convincing data come from the large SWOG 8894 trial. Patients who have only nodal metastases or pelvic and axial bone

metastases have been classified as having minimal disease, compared to those with visceral metastases or appendicular bone metastases, leading to a median overall survival of 58 and 30 months, respectively (1). An updated more precise classification has been published (2), which discriminates patients into three groups according to survival, with a median OS of 54, 30 and 21 months, respectively.

Table 18: Prognostic factors for the heterogeneous M1 population for patients with advanced prostate cancer (2)

Prognostic factors	Good		Intermediate		Poor
Axial bone metastasis and/or nodes	X				
Appendicular bone or visceral metastasis		X	X	X	X
Performance status < 1		X	X		
Performance status ≥1				X	X
Gleason score < 8		X			
Gleason score ≥ 8			X		
PSA < 65				X	
PSA ≥ 65					X

13.2 First-line hormonal treatment

Primary androgen deprivation therapy (ADT) is the standard of care, usually with a long-lasting LHRH analogue or antagonist (3). Orchidectomy is still a valid option provided it has been accepted by the patient. There is not yet any convincing data to choose between an LHRH analogue or antagonist, except in patients with an impending spinal cord compression for whom a bilateral orchidectomy or an LHRH-antagonist should be considered first.

*13.2.1 **Prevention of flare-up***

When choosing an LHRH analogue, an initial testosterone flare-up is likely. It is important to prevent a flare in symptomatic patients or in patients for whom a clinical flare might lead to severe complications. However, there is little data to support the long-term impact of preventing a flare-up, as has been suggested (4).

The concomitant administration of an anti-androgen is used to prevent testosterone flare-up. It has been suggested that giving an anti-androgen at the same time as the LHRH analogue may be sufficient to prevent flare-up rather than giving an anti-androgen for some days before treatment is started with an LHRH analogue (5). However, there has been no trial specifically designed to decide the best choice of anti-androgen or modality.

13.3 Combination therapies

*13.3.1 **Complete androgen blockade (CAB)***

Although castration reduces serum testosterone levels by up to 95%, an intraprostatic androgen stimulus is sustained by the conversion of circulating androgens of adrenal origin into DHT within the prostate cells. However, the action of the adrenal androgens can be blocked by adding an anti-androgen to either surgical or pharmacological castration, a concept known as complete (or maximal or total) androgen blockade (CAB).

The many studies comparing CAB with monotherapy have produced conflicting results (6). The largest randomized trial compared surgical castration, with or without flutamide, in 1286 M1b patients. No difference was observed between both groups (1). According to the most recent systematic reviews and meta-analyses, at a follow-up of 5 years, CAB appears to provide a small survival advantage (< 5%) versus monotherapy (7-10) (LE: 1a). However, some of the largest trials included were methodologically flawed (61). It remains debatable whether this small advantage, if any, is useful in everyday clinical practice, as the survival benefit seems limited to patients taking non-steroidal anti-androgens (12) and only appears after 5 years of follow-up.

Gastrointestinal, ophthalmological and haematological side effects are worse with CAB. Although LHRH analogues and non-steroidal anti-androgens have the highest estimated quality-adjusted survival, there is an incremental cost of more than US$1 million per quality-adjusted life-year for CAB over orchiectomy alone.

*13.3.2 **Non-steroidal antiandrogen (NSAA) monotherapy***

13.3.2.1 Nilutamide

There are no comparative trials of nilutamide monotherapy with castration or with other anti-androgens. Nilutamide is not licensed for monotherapy.

13.3.2.2 Flutamide

Early phase II trials suggested the efficacy of flutamide monotherapy in advanced PCa. The main advantage suggested was the preservation of sexual function in up to 80% of patients with no pre-treatment erectile dysfunction. This finding has not been confirmed in the EORTC trial 30892 (13), in which as few as 20% of men treated with flutamide maintained sexual activity for up to 7 years.

In the only published RCT, there was no significant difference in OS for flutamide monotherapy compared to castration in M1b patients with a PSA < 100 ng/mL (14). At a higher PSA, flutamide was inferior. However, the trial was underpowered. Results are still awaited from an ongoing Swedish study, which randomized 700 patients with M1 PCa to flutamide, 250 mg three times daily, or CAB (15).

13.3.2.3 Bicalutamide

Dose-finding studies established that bicalutamide, 150 mg once daily, was chosen for further evaluation, as both primary and adjuvant monotherapy (16). It has been compared to medical or surgical castration in two large prospective RCTs with identical study designs, including a total of 1435 patients with locally advanced M0 or M1 PCa (17). A pooled analysis showed:

- In M1 patients, there was an improvement in OS with castration, although the difference in median survival between the groups was only 6 weeks (17).
- In M0 patients (n = 480), no significant difference was noted in OS (18) based on the Kaplan-Meier test, with median survival being 63.5 months in the bicalutamide arm compared with 69.9 months in the castration one.

In two smaller RCTs, high-dose bicalutamide was compared with CAB. In the first trial (251 patients with predominantly M1 stage), there was no apparent difference in OS (19). In the second trial (220 patients with M0 and M1 stage), there was no difference in OS for well-differentiated tumours (G1) or tumours that were only moderately differentiated (20) (G2) (LE: 1b). However, both studies were underpowered and the first study has not yet been fully published.

High-dose bicalutamide has emerged as an alternative to castration for highly selected, well-informed patients with M1 PCa with a low PSA (21). However, the expected benefit of bicalutamide for QoL compared with castration is far from being proven.

13.3.3 ***Intermittent versus continuous ADT***

For reasons we are beginning to understand, long-term CAB, which stimulates prostate cell apoptosis, fails to eliminate the entire malignant cell population. Thus, after a variable period (averaging 24 months), the tumour inevitably relapses, characterized by a castrate-independent state of growth. Experimental data indicate that castrate-independent progression may begin early after the administration of hormonal therapy, coinciding with the cessation of androgen-induced differentiation of stem cells (22). It has therefore been suggested that stopping androgen deprivation prior to progression of androgen-independent cells would mean any subsequent tumour growth would be solely sustained by the proliferation of androgen-dependent stem cells. The stem cells should therefore be susceptible once again to androgen withdrawal. Thus, intermittent androgen blockade (IAD) would delay the emergence of the androgen-independent clone. It should be noted that this rationale has been developed mainly through models (e.g. the Shionoggi model), which may be significantly different to the behaviour of total tumour in men. Other possible benefits of IAD include the preservation of QoL in off-treatment periods and a reduction in the cost of treatment.

A detailed systematic review was recently published (23). It concluded that intermittent IAD was feasible and accepted by patients. However, RCTs are required to clarify the potential survival benefit suggested by animal models.

Overall, nine RCTs are underway, only some of which have published findings. Most of the trials have included a mixed patient population of both locally advanced and metastatic disease, with two trials including only metastatic patients. Results from one of the largest trials (SWOG 9346) (n = 1535), which included only randomized metastatic patients, has been presented, but is not yet published (24). Few fully published trials are available. All the trials that have published results have reported similar findings, except for one trial, allowing the inclusion of abstract-only references.

13.3.3.1 Summary of important trial results in IAD in locally advanced or metastatic PCa

Research in mixed populations of locally advanced and metastatic PCa (25-27):

- There has never been a suggestion of decreased survival using IAD. To date, the largest first fully

published trial (n = 766) was carried out by the South European Uroncological (SEUG) Group (28) with 30% M1. The primary end-point was time to progression. After a median follow-up of 51 months, there was no difference in either time to progression (HR: 0.81; p = 0.11) or OS (HR: 0.99). The metastatic status and PSA at randomization were associated with specific death rates. No overall QoL benefit was seen, except for more frequent side effects in the CAB-treated group.

- However, there was a clear benefit for improved sexual function in the IAD group versus the CAB group, with 28% sexually active vs 10% at 15 months after randomization, respectively. After a median of 7 years' follow-up, it should be highlighted that both the IAD treatment arm and the continuous treatment arm showed similar non-significant specific death increases. The second largest study (27) randomized 554 out of 852 patients with either M1 disease (50%) or a locally advanced disease. After a median follow-up of 65 months, no significant difference was observed in the median PFS (34.5 months in the IAD group vs 30.2 months in the CAB group, p = 0.29) in either the total study population or in the N+ or M1 subgroup populations. The median OS was 45 months in both groups.

Research in M1b patients:

- The only published trial on M1b patients included a very small number of patients (n = 341) (29). Again, neither OS nor PFS were different between both arms. However, this trial was clearly underpowered.
- Detailed results are awaited from the SWOG trial 9346, which randomized 1134 men out of 3040 men with stage D2 PCa to intermittent and continuous ADT. This is the largest trial that has been conducted in PCa and findings were first presented at ASCO in 2012. It is a non-inferiority trial, which means that for the first time IAD was presented as being not 'non inferior' compared to continuous ADT (median OS 5.1 years for IAD compared to 5.8 years for the continuous treatment arm). Although not yet published, results from this trial have raised the question for the first time of the safety of IAD in metastatic situations (24).
- In 1386 patients relapsing after radiotherapy, the randomized JPR.7 trial has shown no difference in OS after a median follow up of 6.9 years, suggesting that this treatment modality might become the standard for those requiring ADT treatment. The median OS were 8.8 years in the IAD compared to 9.1 years in the continuous treatment arm (HR = 1.02; 0.86-1.21) (30).

IAD regimen of fixed 6-month periods of CAB treatment and surveillance:
An alternative IAD regimen using fixed 6-month periods of CAB treatment and surveillance has been published (31). The results are limited by the small number of patients (n = 129). There was no difference observed in OS, cancer-specific survival or PFS after a mean 44.8 months of follow up.

13.3.3.2 Potential benefits of IAD

Intermittent androgen deprivation has not been shown to be associated with prolonged hormone-sensitive status or an increase in OS. However, this modality is well accepted by patients, urologists and oncologists. Although the QoL benefit is less than expected or absent, except in a few studies (30,32,33), IAD is better tolerated and sometimes benefits sexual functioning (26,28). Other possible long-term benefits, which are not clearly proven, include bone protection (34,35) and/or a protective effect against metabolic syndrome. Testosterone recovery is seen in most studies (23), leading to an intermittent castration (not just an intermittent treatment delivery).

13.3.3.3 Optimal threshold for stopping or resuming ADT

The optimal thresholds at which ADT must be stopped or resumed are empirical (23). The best candidates for IAD have still not been completely defined (23,35), but are probably patients with locally advanced or relapsing disease, provided a perfect response is obtained (see below). Nevertheless, several points are clear (23,36).

- Because IAD is based on intermittent castration, only drugs leading to castration are suitable for use in IAD.
- It is unclear if an LHRH agonist may be used alone, as published experiences are based on CAB. An LHRH antagonist might be a valid alternative, provided clear results are obtained from RCTs.
- The initial (induction) cycle must last between 6 and 9 months, otherwise testosterone recovery is unlikely.
- The treatment is stopped only if patients have fulfilled all the following criteria:
  - well-informed and compliant patient
  - no clinical progression, i.e. a clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease, or 0.5 ng/mL in relapsing disease.
- Strict follow-up must be applied once treatment has stopped, with clinical examination every 3-6 months. The more advanced the disease, the closer should be the follow-up. The PSA level should be measured by the same laboratory to ensure standardization of testing.

- Treatment is resumed when the patient reaches either a clinical progression, or a PSA value above a predetermined, empirically fixed, threshold. This is usually 4-10 ng/mL in non-metastatic situations or 10-15 ng/mL in metastatic patients (35).
- The same treatment is used for at least 3-6 months.
- Subsequent cycles of treatment are based on the same rules until the first sign is seen of hormone-refractory status.

In conclusion, IAD is currently widely offered to patients with PCa in various clinical settings and its status should no longer be regarded as investigational (LE: 2). Future publication of the results from the SWOG 9346 may change guidance on the use of IAD in M1B patients.

*13.3.4 **Immediate versus deferred ADT***

There is no discussion regarding symptomatic patients. However, it is still unclear when it is the most appropriate time to introduce hormonal therapy in asymptomatic patients with metastatic PCa. Should hormonal therapy be introduced immediately or deferred until there are signs and symptoms of clinical progression? The controversy has arisen because of the lack of properly conducted RCTs. Published studies have not included enough patients and have been underpowered, with heterogeneity of patient enrolment (i.e. locally advanced, nodal and metastatic stages of disease), and with variation in the hormonal treatments given and in the follow-up schedules and modalities used.

A report by the Agency for Health Care Policy and Research (AHCPR) indicated a possible survival advantage for early ADT in single studies in which hormonal treatment was the primary therapy (37). Furthermore, androgen suppression was shown to be the most cost-effective therapy if it was begun after patients had experienced symptoms from metastatic disease (38). The Cochrane Library review extracted four good-quality RCTs; these were namely VACURG I and II studies, the MRC trial and the ECOG 7887 study, which were all conducted in the pre-PSA era. The studies included patients with advanced PCa, who had received early versus deferred ADT, either as primary therapy or adjuvant to radical prostatectomy (39).

In M1a/b patients only, no improvement in OS was observed, although early ADT significantly reduced disease progression and complication rates due to progression. However, the results were different in locally advanced situations with a relatively small benefit in OS. There was an absolute risk reduction of 5.5% after 10 years (39), while another review reported an OS benefit (+10%) and SS (+20%) (40), especially in combination with a local treatment. In the PSA era, the EORTC 30891 study (41) has clarified the results a small benefit in OS, but not for cancer-specific survival. Furthermore, only young patients with a high PSA are likely to clearly benefit.

Based on a systematic review of the literature, recently published ASCO guidelines on initial hormonal treatment for androgen-sensitive, metastatic, recurrent or progressive PCa concluded that no recommendation can be made about when to start hormonal therapy in advanced asymptomatic PCa, (42). The ESMO guidelines do not make any statement (43).

For asymptomatic metastatic patients, an active clinical surveillance protocol may be an acceptable option in clearly informed patients if survival is the main objective.

The detailed discussion on immediate or deferred ADT combined with surgery or radiation therapy is discussed in Sections 8.3 and 10.3.

13.4 Indications for hormonal therapy

Table 19 lists the indications for hormonal therapy.

Table 19: Indications for hormonal therapy in metastatic patients

Castration	Benefits	LE
M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis)	1b
	Even without a RCT, this is the standard of care and must be applied and considered as level 1 evidence	1
M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications	1b

	An active clinical surveillance protocol may be an acceptable option in clearly informed patients if survival is the main objective	3
Anti-androgens		
Short-term administration	To reduce the risk of the 'flare-up' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist (91,92)	1b
	It may be sufficient to give an anti-androgen for 3 weeks of concomitant use, starting treatment on the same day as LHRH analogue treatment is started, or for up to 7 days before the first LHRH analogue injection	4
Long-term administration	This is an option in highly selected and motivated patients with a low PSA	3
Intermittent treatment		
Threshold to start and stop ADT	The threshold is empirically chosen. However, it should reproduce what has been used in clinical trials. In trials, treatment is usually stopped when the PSA level is < 4 ng/mL (M1) and < 0.5-4 ng/mL (relapsing)	4
	Treatment is usually re-started when the PSA is > 4-10 (relapsing) and > 10-15 ng/mL (M1)	
Drug	LHRH analogue + flare-up prevention OR combined treatment	1
Population:	Metastatic patients: asymptomatic, motivated, with a clear PSA response after the induction period.	2*
	Relapsing after radiotherapy: patients with a clear response after the induction period	1b

** Based on one published trial in M1b patients only and two published cohorts in mixed populations.*

13.5 Contraindications for various therapies (Table 20)

Table 20: Contraindications for various therapies.

Therapy	Contraindications
Bilateral orchiectomy	Psychological reluctance to undergo surgical castration
Oestrogens	Known cardiovascular disease
LHRH agonists alone	Patients with metastatic disease at high risk for clinical 'flare-up' phenomenon
Anti-androgens	Localised PCa as primary therapy

13.6 References

1. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998 Oct; 339(15):1036-42. http://www.ncbi.nlm.nih.gov/pubmed/9761805
2. Glass TR, Tangen CM, Crawford ED, et al. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. J Urol 2003 Jan;169(1):164-9. http://www.ncbi.nlm.nih.gov/pubmed/12478127
3. Pagliarulo V, Bracarda S, Eisenberger MA, et al. Contemporary role of androgen deprivation therapy for prostate cancer. Eur Urol 2012 Jan; 61(1):11-25. http://www.ncbi.nlm.nih.gov/pubmed/21871711
4. Collette L, Studer UE, Schröder FH, et al. Why phase III trials of maximal androgen blockade versus castration in M1 prostate cancer rarely show statistically significant differences. Prostate 2001 Jun; 48(1):29-39. http://www.ncbi.nlm.nih.gov/pubmed/11391684
5. Tsushima T, Nasu Y, Saika T, et al. Optimal starting time for flutamide to prevent disease flare in prostate cancer patients treated with a gonadotropin-releasing hormone agonist. Urol Int. 2001;66(3):135-9. http://www.ncbi.nlm.nih.gov/pubmed/11316974
6. Moul JW. Twenty years of controversy surrounding combined androgen blockade for advanced prostate cancer. Cancer 2009 Aug;115(15):3376-8. http://www.ncbi.nlm.nih.gov/pubmed/19484788

7. [No authors listed] Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. Lancet 2000 Apr;355(9214):1491-8. http://www.ncbi.nlm.nih.gov/pubmed/10801170
8. Schmitt B, Bennett C, Seidenfeld J, et al. Maximal androgen blockade for advanced prostate cancer. Cochrane Database Syst Rev 2000;(2):D001526. http://www.ncbi.nlm.nih.gov/pubmed/10796804
9. Schmitt B, Wilt TJ, Schellhammer PF, et al. Combined androgen blockade with non-steroidal antiandrogens for advanced prostate cancer: a systematic review. Urology 2001 Apr;57(4):727-32. http://www.ncbi.nlm.nih.gov/pubmed/11306391
10. Samson DJ, Seidenfeld J, Schmitt B, et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer 2002 Jul;95(2):361-76. http://www.ncbi.nlm.nih.gov/pubmed/12124837
11. Collette L, Studer UE, Schroder FH, et al. Why phase III trials of maximal androgen blockade versus castration in M1 prostate cancer rarely show statistically significant differences. Prostate 2001 Jun;48(1):29-39. http://www.ncbi.nlm.nih.gov/pubmed/11391684
12. Akaza H, Hinotsu S, Usami M, et al. Study Group for the Combined Androgen Blockade Therapy of Prostate Cancer. Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. Cancer 2009 Aug;115(15):3437-45. http://www.ncbi.nlm.nih.gov/pubmed/19536889
13. Schroder FH, Whelan P, de Reijke TM, et al. Metastatic prostate cancer treated by flutamide versus cyproterone acetate. Final analysis of the 'European Organization for Research and Treatment of Cancer' (EORTC) Protocol 30892. Eur Urol 2004 Apr;45(4):457-64. http://www.ncbi.nlm.nih.gov/pubmed/15041109
14. Boccon-Gibod L, Fournier G, Bottet P, et al. Flutamide versus orchidectomy in the treatment of metastatic prostate carcinoma. Eur Urol 1997;32(4):391-5. http://www.ncbi.nlm.nih.gov/pubmed/9412794
15. Iversen P. Antiandrogen monotherapy: indications and results. Urology 2002;60(3 Suppl 1):64-71. http://www.ncbi.nlm.nih.gov/pubmed/12231053
16. Kolvenbag GJ, Nash A. Bicalutamide dosages used in the treatment of prostate cancer. Prostate 1999 Apr;39(1):47-53. http://www.ncbi.nlm.nih.gov/pubmed/10221266
17. Tyrrell CJ, Kaisary AV, Iversen P, et al. A randomized comparison of 'Casodex' (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol 1998;33(5):447-56. http://www.ncbi.nlm.nih.gov/pubmed/9643663
18. Iversen P, Tyrrell CJ, Kaisary AV, et al. Bicalutamide monotherapy compared with castration in patients with non-metastatic locally advanced prostate cancer: 6.3 years of follow up. J Urol 2000 Nov;164(5):1579-82. http://www.ncbi.nlm.nih.gov/pubmed/11025708
19. Fourcade RO, Chatelain C, Poterre M, et al. An open multicentre randomized study to compare the effect and safety of 'Casodex' (bicalutamide) 150 mg monotherapy with castration plus nilutamide in metastatic prostate cancer. Eur Urol 1998;33(Suppl 1):88,349A.
20. Boccardo F, Barichello M, Battaglia M, et al. Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer: updated results of a multicentric trial. Eur Urol 2002 Nov;42(5):481-90. http://www.ncbi.nlm.nih.gov/pubmed/12429158
21. Loblaw DA, Mendelson DS, Talcott JA, et al: American Society of Clinical Oncology. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. J Clin Oncol 2004 Jul;22(14):2927-41. http://www.ncbi.nlm.nih.gov/pubmed/15184404
22. Bruchovsky N, Rennie PS, Coldman AJ, et al. Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma. Cancer Res 1990 Apr;50(8):2275-82. http://www.ncbi.nlm.nih.gov/pubmed/2317815
23. Abrahamsson PA. Potential benefits of intermittent androgen suppression therapy in the treatment of prostate cancer: a systematic review of the literature. Eur Urol 2010 Jan;57(1):49-59. http://www.ncbi.nlm.nih.gov/pubmed/19683858

24. Hussain M, Tangen CM, Higano CS, et al. Intermittent (IAD) versus continuous androgen deprivation (CAD) in hormone sensitive metastatic prostate cancer (HSM1PC) patients (pts): results of SWOG 9346 (INT-0162), an international phase III trial. J Clin Oncol 30, 2012 (suppl; abstr 4). http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=92516
25. de Leval J, Boca P, Yousef E, et al. Intermittent versus continuous total androgen blockade in the treatment of patients with advanced hormone-naive prostate cancer: results of a prospective randomized multicenter trial. Clin Prostate Cancer 2002 Dec;1(3):163-71. http://www.ncbi.nlm.nih.gov/pubmed/15046691
26. Miller K, Steiner U, Lingnau A, et al. Randomised prospective study of intermittent versus continuous androgen suppression in advanced prostate cancer. J Clin Oncol 2007;Part 1;25(18S), abstract 5015. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=33936
27. Salonen AJ, Taari K, Ala-Opas M, et al. The FinnProstate Study VII: intermittent versus continuous androgen deprivation in patients with advanced prostate cancer. J Urol 2012 Jun;187(6):2074-81. http://www.ncbi.nlm.nih.gov/pubmed/22498230
28. Calais da Silva FE, Bono AV, Whelan P, et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Uroncological Group. Eur Urol 2009 Jun;55(6):1269-77. http://www.ncbi.nlm.nih.gov/pubmed/19249153
29. Mottet N, van Damme J, Loulidi S, et al. Intermittent hormonal therapy in the treatment of metastatic prostate cancer: a randomized trial. BJU Int 2012 Nov; 110(9):1262-9. http://www.ncbi.nlm.nih.gov/pubmed/22502816
30. Crook JM, O'Callaghan CJ, Ding K, et al. A phase III randomized trial of intermittent versus continuous androgen suppression for PSA progression after radical therapy (NCIC CTG PR.7/SWOG JPR.7/CTSU JPR.7/ UK Intercontinental Trial CRUKE/01/013). J Clin Oncol 29: 2011 (suppl; abstr 4514) http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=102&abstractID=77775
31. Irani J, Celhay O, Hubert J, et al. Association for Research in Urological Oncology. Continuous versus six months a year maximal androgen blockade in the management of prostate cancer: a randomized study. Eur Urol 2008 Aug;54(2):382-91. http://www.ncbi.nlm.nih.gov/pubmed/18339475
32. Verhagen PCMS, Wissenburg LD, Wildhagen MF, et al. Quality of life effects of intermittent and continuous hormonal therapy by cyproterone acetate (CPA) for metastatic prostate cancer. Eur Urol Suppl 2008;7(3):206, abstract 541.
33. Salonen AJ, Taari K, Ala-Opas M, et al. the FinnProstate Group. Advanced prostate cancer treated with intermittent or continuous androgen deprivation in the randomised FinnProstate Study VII: quality of life and adverse effects. Eur Urol 2013 Jan;63(1):111-120. http://www.ncbi.nlm.nih.gov/pubmed?term=22857983
34. Higano C, Shields A, Wood N, et al. Bone mineral density in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. Urology 2004 Dec;64(6):1182-6. http://www.ncbi.nlm.nih.gov/pubmed/15596194
35. Shaw GL, Wilson P, Cuzick J, et al. International study into the use of intermittent hormone therapy in the treatment of carcinoma of the prostate: a meta-analysis of 1446 patients. BJU Int 2007 May;99(5):1056-65. http://www.ncbi.nlm.nih.gov/pubmed/17346277
36. Boccon-Gibod L, Hammerer P, Madersbacher S, et al. The role of intermittent androgen deprivation in prostate cancer. BJU Int 2007 Oct;100(4):738-43. http://www.ncbi.nlm.nih.gov/pubmed/17662079
37. Seidenfeld J, Samson DJ, Aronson N, et al. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostate cancer. Evidence Report/Technology Assessment No. 4. AHCPR Publication No. 99-E0012, May 1999, Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services, Rockville, MD. http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.chapter.5028
38. Bayoumi AM, Brown AD, Garber AM. Cost-effectiveness of androgen suppression therapies in advanced prostate cancer. J Natl Cancer Inst 2000 Nov;92(21):1731-9. http://www.ncbi.nlm.nih.gov/pubmed/11058616
39. Nair B, Wilt T, MacDonald R, et al. Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. Cochrane Database Syst Rev 2002;(1):CD003506. http://www.ncbi.nlm.nih.gov/pubmed/11869665

40. Verhagen PC, Schröder FH, Collette L, et al. Does local treatment of the prostate in advanced and/or lymph node metastatic disease improve efficacy of androgen-deprivation therapy? A systematic review. Eur Urol 2010 Aug;58(2):261-9. http://www.ncbi.nlm.nih.gov/pubmed/20627403
41. Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006 Apr;24(12):1868-76. http://www.ncbi.nlm.nih.gov/pubmed/16622261
42. Loblaw DA, Mendelson DS, Talcott JA, et al: American Society of Clinical Oncology. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. J Clin Oncol 2004 Jul;22(14):2927-41. http://www.ncbi.nlm.nih.gov/pubmed/15184404
43. Horwich A, Parker C, Bangma C, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010 May; Suppl 5:v129-33. http://www.ncbi.nlm.nih.gov/pubmed/20555062

14. MANAGEMENT OF PROSTATE CANCER IN OLDER MEN

14.1 Introduction

Prostate cancer is the most prevalent cancer in men, with a median age at diagnosis of 68 years. Two-thirds of prostate cancer-related deaths occur in men aged ≥ 75 years (1). Older men tend to have larger tumours of a higher grade than younger patients (2,3). Treatment decisions for older men should take into consideration the risk of dying from PCa (which depends on the grade and stage of the tumour), potential adverse effects of treatment, and patient preference. Interventions that might decrease health-related quality of life (HRQoL) without prolonging survival should be avoided. Evidence suggests that in both the USA (4) and Europe (5) older patients are under-treated: only a minority of older adults with localised prostate cancer receive curative treatment. However, curative treatment should neither be denied where appropriate, nor limited to androgen deprivation therapy (ADT).

Life expectancy is a major determinant of the potential for benefit from therapy. The International Society of Geriatric Oncology (SIOG) Prostate Cancer Working Group recommends that the decision-making process for treating older men with PCa should be based on a systematic evaluation of health status, most importantly comorbidities, dependence status, and nutritional status (6). These factors influence patient survival and can also affect the ability to tolerate treatment-related side-effects (6).

For localised disease, treatment benefit is usually considered to be seen only beyond 10 years, which leads to a treatment frontier of 75 years. This should be reconsidered, given that Walter (7) has shown that survival probability is linked not only to legal age, but more importantly to overall health status. For example, a healthy 80-year-old senior can expect a median 10.8 years of survival, compared to 6.7 years for a vulnerable, and 3.3 years for a frail senior. At 85 years of age, healthy seniors can expect to survive 8 years. These figures date back 10 years, and are likely to have increased with life expectancy.

Comorbidity is a major predictor of PCa mortality. Tewari *et al*. demonstrated that comorbidity evaluated by the Charlson index was the strongest predictor of death from causes other than PCa in men with localised PCa treated with RP (8). This was recently confirmed in a cohort of patients from the Surveillance, Epidemiology and End Results (SEER) database, all of whom had treatment-resistant PCa. At 10 years, most men with a Charlson score ≥ 2 died from competing causes, irrespective of age or tumour aggressiveness (9). Currently the Cumulative Illness Score Rating-Geriatrics (CISR-G) is the best available tool for assessing the risk for death unrelated to PCa. Whereas the Charlson index considers only potentially lethal comorbid conditions, the CISR-G also rates nonlethal conditions according to their severity and level of control (10,11).

Level of dependence in daily activities is another factor that influences survival in senior adult patients (12,13). Dependence can be evaluated using the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales. The ADL scale rates an ability to accomplish basic activities of daily living, while the IADL scale rates activities that require a higher level of cognition and judgement (for example the ability to manage money or medication, or to use transportation or the telephone).

Malnutrition has also been shown to be associated with an increased mortality rate in senior patients (14). Nutritional status can be estimated by the variation of weight during the previous 3 months:

- good nutritional status < 5% of weight loss;
- risk of malnutrition - weight loss 5-10%;
- severe malnutrition - weight loss > 10%.

Evaluation of comorbidity, dependence and malnutrition is recommended by The SIOG Prostate Cancer Working Group in order to classify patients into one of 4 groups:

1. 'Fit' or 'healthy' older men should receive the same standard treatment as younger patients.
2. 'Vulnerable' patients (i.e. reversible impairment) should receive standard treatment after resolution of any geriatric problems through geriatric interventions.
3. 'Frail' patients (i.e. irreversible impairment) should receive an adapted treatment.
4. Patients who are 'too sick' with 'terminal illness' should receive only symptomatic palliative treatment (6).

"Fit" and "vulnerable" older men with localised PCa in the high-risk group defined by D`Amico *et al*. (18), with a chance of surviving for more than 10 years are likely to benefit from curative treatment. Older men in the low risk and possibly intermediate risk classification are most likely to benefit from a watchful-waiting approach. The urological approach in older men with PCa should be the same as in younger patients, based on existing recommendations (15-17). Older men with PCa should be managed according to their individual health status which is mainly driven by the severity of associated comorbid conditions and not according to chronological age.

14.2 Treatment-related complications

The risk of short-term postoperative complications appears to be related more to the severity of comorbidities than chronological age. Conversely, the risk of long-term incontinence after RP is more influenced by increasing age than comorbidity (19,20). EBRT has similar outcomes in terms of cancer control and treatment related comorbidities in both older and younger patients, assuming a dose of ≥ 70Gy using intensity modulated radiotherapy (IMRT) or image guided radiotherapy (IGRT). Brachytherapy might be a suitable option in older patients, but survival benefit in older men with low risk disease has not been established. Urinary, bowel, and erectile complications after brachytherapy increase significantly with both increasing age and severity of comorbidities (15). For those with locally advanced disease, a combined modality of EBRT and long term hormonal treatment must be considered. The drawback of ADT in older patients has been discussed earlier (see Chapter 14). Cardiac status should be specially checked if ADT is considered, as it might be associated with increased morbidity, but not mortality. Comorbidity by itself could also be a discriminating factor, as suggested recently in localised high risk patients (21).

In patients with non-metastatic localised PCa unsuitable for curative treatment, immediate ADT should be used only in patients requiring symptom palliation (22,23). In the case of locally advanced T3-T4 disease immediate ADT can be of benefit in patients with PSA > 50ng/mL and PSA doubling time of < 12 months (22,23). ADT is the first-line treatment in hormone-sensitive metastatic PCa. The SIOG Prostate Cancer Working Group recommends evaluation of bone mineral status and prevention of osteoporosis. All men receiving ADT should receive calcium and vitamin D supplementation. The routine use of biphosphonates to prevent skeletal complications in patients undergoing ADT is not recommended unless there is a documented risk for fracture or castration-resistant PCa with skeletal metastasis (6). However, in a recent randomised trial Denosumab was shown to improve metastases free survival in patients without distant metastases and rising PSA (29.5 months vs 25.2 months, p = 0.0028) and increase time to first bone lesion (33.2 months vs 29.5 months, p = 0.0032) (24).

In metastatic castration-resistant prostate cancer (CRPC), chemotherapy with docetaxel (75 mg/m^2 every 3 weeks) is the standard for fit and vulnerable older men. The tolerability of the docetaxel 3-weekly regimen has not been specifically studied in frail older men. In a retrospective analysis of 175 patients aged ≥ 75 years treated with docetaxel, patients with a good performance status responded to docetaxel therapy to a similar extent as younger patients. Docetaxel was generally well tolerated. The weekly regimen showed less febrile neutropenia than the 3-weekly regimen but a higher rate of fatigue, resulting in frequent treatment discontinuation (25). The place of weekly docetaxel in metastatic CRPC should be further evaluated. Palliative treatments in CRPC include palliative surgery, radiopharmaceuticals, EBRT, and medical treatments for pain and symptoms.

14.3 References

1. Ries LAG, Melbert D, Krapcho M et al. eds. SEER Cancer Statistics Review, 1975-2005. Bethesda, MD: National Cancer Institute, 2008. Available at: http://seer.cancer.gov/csr/1975-2005/, based on December 2009 SEER data submission.

2. Richstone L, Bianco FJ, Shah HH, et al. Radical prostatectomy in men aged >or=70 years: effect of age on upgrading, upstaging, and the accuracy of a preoperative nomogram. BJU Int 2008 Mar;101(5):541-6.
http://www.ncbi.nlm.nih.gov/pubmed/18257855
3. Sun L, Caire AA, Robertson CN, et al. Men older than 70 years have higher risk prostate cancer and poorer survival in the early and late prostate specific antigen eras. J Urol 2009 Nov;182(5):2242-8.
http://www.ncbi.nlm.nih.gov/pubmed/19758616
4. Bubolz T, Wasson JH, Lu-Yao G, et al. Treatments for prostate cancer in older men: 1984-1997. Urology 2001 Dec;58(6):977-82.
http://www.ncbi.nlm.nih.gov/pubmed/11744472
5. Houterman S, Janssen-Heijnen ML, Hendrikx AJ, et al. Impact of comorbidity on treatment and prognosis of prostate cancer patients: a population-based study. Crit Rev Oncol Hematol 2006 Apr;58(1):60-7.
http://www.ncbi.nlm.nih.gov/pubmed/16213153
6. Droz JP, Balducci L, Bolla M, et al. Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology. BJU Int 2010 Aug;106(4):462-9.
http://www.ncbi.nlm.nih.gov/pubmed/20346033
7. Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA 2001 Jun 6;285(21):2750-6.
http://www.ncbi.nlm.nih.gov/pubmed/11386931
8. Tewari A, Johnson CC, Divine G, et al. Long-term survival probability in men with clinically localized prostate cancer: a case-control, propensity modeling study stratified by race, age, treatment and comorbidities. J Urol 2004 Apr;171(4):1513-9.
http://www.ncbi.nlm.nih.gov/pubmed/15017210
9. Albertsen PC, Moore DF, Shih W, et al. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol 2011 Apr 1;29(10):1335-41.
http://www.ncbi.nlm.nih.gov/pubmed/21357791
10. Extermann M. Measuring comorbidity in older cancer patients. Eur J Cancer 2000 Mar;36(4):453-71.
http://www.ncbi.nlm.nih.gov/pubmed/10717521
11. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968 May;16(5):622-6.
http://www.ncbi.nlm.nih.gov/pubmed/5646906
12. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963 Sep;185:914-9.
http://www.ncbi.nlm.nih.gov/pubmed/14044222
13. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969 Autumn;9(3):179-86.
http://www.ncbi.nlm.nih.gov/pubmed/5349366
14. Blanc-Bisson C, Fonck M, Rainfray M, et al. Undernutrition in elderly patients with cancer: target for diagnosis and intervention. Crit Rev Oncol Hematol 2008 Sep;67(3):243-54.
http://www.ncbi.nlm.nih.gov/pubmed/18554922
15. Heidenreich A, Bellmunt J, Bolla M, et al. [EAU guidelines on prostate cancer. Part I: screening, diagnosis, and treatment of clinically localised disease.] Actas Urol Esp 2011 Oct;35(9):501-14. [Article in Spanish]
http://www.ncbi.nlm.nih.gov/pubmed/21757259
16. Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol 2007 Jun;177(6):2106-31.
http://www.ncbi.nlm.nih.gov/pubmed/17509297
17. National Comprehensive Cancer Network. NCCN Clinical Cancer for senior adult oncology. V.1.2012. Available at: http://www.nccn.org/professionals/ physician_gls/f_guidelines.asp.
18. D'Amico AV, Moul J, Carroll PR, et al. Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. J Clin Oncol 2003 Jun;21(11):2163-72.
http://www.ncbi.nlm.nih.gov/pubmed/12775742
19. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002 Apr;346(15):1138-44.
http://www.ncbi.nlm.nih.gov/pubmed/11948274
20. Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. JAMA 2000 Jan 19;283(3):354-60.
http://www.ncbi.nlm.nih.gov/pubmed/10647798

21. D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA 2008 Jan;299(3):289-95. http://www.ncbi.nlm.nih.gov/pubmed/18212313
22. Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006 Apr 20;24(12):1868-76. http://www.ncbi.nlm.nih.gov/pubmed/16622261
23. Studer UE, Collette L, Whelan P, et al. Using PSA to guide timing of androgen deprivation in patients with T0-4 N0-2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). Eur Urol 2008 May;53(5):941-9. http://www.ncbi.nlm.nih.gov/pubmed/18191322
24. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006 Sep 20;24(27):4448-56. http://www.ncbi.nlm.nih.gov/pubmed/16983113
25. D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol 2007 Jun 10;25(17):2420-5. http://www.ncbi.nlm.nih.gov/pubmed/17557956

15. QUALITY OF LIFE OF PATIENTS WITH LOCALISED PROSTATE CANCER

15.1 Introduction

The increase in life expectancy of patients with localised PCa has made the quality of life (QoL) after treatment a key issue for PCa survivors. The term 'health-related quality of life' (HRQoL) is typically used to refer to the impact that disease and treatment have on a person's well-being and physical, emotional and social functioning, including daily functioning (1-4). HRQoL is a patient-centred outcome, which is rated by the patient himself, particularly as physicians often underestimate the impact of disease and treatment on their patients' lives (5).

In PCa, HRQoL is usually divided into PCa-specific and PCa-general issues. PCa-specific HRQoL refers to the disease-specific outcome of PCa, including urinary, bowel, and sexual functioning. PCa-general HRQoL refers to the generic issues of well-being, including physical, social, emotional, and cognitive functioning, vitality/fatigue, pain, general health status, global QoL and life satisfaction (6).

HRQoL is measured using standardised questionnaires, which collect patient-centric data and provide an objective assessment and perception of both generic and disease-specific domains. Several comprehensive HRQoL questionnaires have undergone validation and have been used to measure early stage PCa outcomes. The most frequently used questionnaires include the EPIC (Expanded Prostate Cancer Index Composite), the Symptom indexes constructed by Clark and Talcott, and the Prostate Module appendix for the EORTC-QLQ C30 (7-9).

Various forms of therapies have different impacts on HRQoL. A comparison of the most common contemporary therapies for localised PCa (radical prostatectomy, brachytherapy, external-beam radiation therapy and active surveillance) is necessary to inform patients about treatment options and to address individual patient preferences for the various possible outcomes. There is still very little objective data about HRQoL for PCa treatment, mainly because of a lack of prospective trials.

15.2 Active surveillance

Although active surveillance avoids treatment-related side effects, it carries an increased risk of psychological distress, which can have significant effects on the patient's HRQoL. There are certain risk factors for patients who may not do well on active surveillance. These factors include the patient's perception that the physician is making most of the decision-making, a poor physical health score, a high neuroticism (anxiety) score, and a high PSA value. All these factors were found to have significant positive associations with lower HRQoL scores in multivariate analysis (10). Anxiety and distress did not increase and remained low during the first 9 months of surveillance in men enrolled in the active surveillance PRIAS study (11). Additional research with a longer follow-up is needed to define the significance of negative effects of active surveillance on HRQoL (LE: 1b).

Data from an RCT on anxiety comparing WW and RP (13) found that depression, well-being and psychological status were not significantly different between treatment groups, even if they were systematically

inferior in the treated group (LE: 1b).

Apart from psychological distress, men left without anticancer treatment may have a higher level of irritative- obstructive urinary symptoms compared to patients treated with RP or RT at 12-36 months of follow-up (14) (LE: 2b).

15.3 Radical prostatectomy

Several trials have shown that RP has a significant negative effect on multiple QoL domains, including a lower sexual function score, lower urinary function and incontinence scores, and a lower physical HRQoL (13,15-17).

In the Prostate Cancer Outcomes Study (PCOS), 8.7% of men at 24 months were bothered by a lack of urinary control and 41.9% reported that sexual function was a moderate-to-big problem in their daily lives (18). Sexual function and interest are the two prostate-specific domains that decline most after surgery and remain most affected after 1 year (19). The recovery of sexual dysfunction and urinary incontinence occurs over 2 to 3 years (20-22). Sanda et al. (15) recently reported that urinary incontinence was at its worst by 2 months after surgery, after which time it improved in most patients. At 1 year after RP, 26% of patients reported that sexual function was a 'big problem', while 76% reported that urinary incontinence was a 'very small' problem or 'no problem at all' (LE: 2a).

Although certain advances have been made that help diminish these side effects, such as nerve-sparing RP or robotic-assisted radical prostatectomy (RALP), their impact on HRQoL remain controversial. Preserving the neurovascular bundles reduces the incidence of impotence (15,23) and can also help to improve urinary function (22,24). Both RALP and open RP have demonstrated comparable functional outcomes and should therefore theoretically have similar HRQoL scores (25). Other general HRQoL domains that may be affected after surgery included pain and energy (18). Several studies have shown that pain and energy worsen immediately post-RP but usually improve by 12 months (20,22,26).

A new methodology for reporting outcomes after RP was proposed recently: the so-called trifecta (27) and pentafecta (28). The new method combines major outcomes, including continence, potency and cancer control (trifecta) and peri-operative complications and positive surgical margins rates (pentafecta). Pentafecta rates reflect post-operative patient expectations and satisfaction more accurately and can be used in counselling patients with clinically localised PCa. The use of trifecta and pentafecta outcomes in post-operative HRQoL assessment needs further validation.

15.4 External-beam radiation therapy (EBRT) and low-dose rate (LDR) brachytherapy

Patients undergoing EBRT and iodine-125 LDR brachytherapy may have urinary, sexual and bowel dysfunction following treatment (29). Both methods can result in irritative voiding symptoms, such as urgency, frequency, and urge incontinence, that negatively affect overall urinary function and HRQoL. The most predominant severe acute toxicity after LDR brachytherapy is urinary retention requiring catheterisation (30). Roeloffzen et al. (30,31) reported that acute urinary retention after LDR brachytherapy occurs in 8-10.2% of patients and has a significant negative impact on patients' HRQoL up to 6 years after treatment, in terms of both global QoL measures and urinary symptom scores (LE: 3).

A prospective multicentre study showed that the effects of EBRT on urinary symptoms had resolved at 12 months and improved over baseline at 24 months (15). In the same study, patients in the LDR brachytherapy group reported significant detriments in urinary irritation or obstruction and incontinence compared with baseline. Incontinence after LDR brachytherapy was reported by 4-6% of patients at 1-2 years after treatment. Eighteen percent of patients in the LDR brachytherapy group and 11% of those in the EBRT group reported moderate or worse distress from overall urinary symptoms at 1 year (15) (LE: 3).

It has been shown that both EBRT and LDR brachytherapy have a significant impact on the bowel and rectal HRQoL domains (15,32). Bowel/rectal problems appeared to have an overall impact almost as important as that of the urinary domain (33,34). The onset of symptoms occurred during or early after treatment, and sometimes persisted into follow-up. Sanda et al. reported rectal urgency, frequency, pain, fecal incontinence, or haematochezia-caused distress related to bowel function in 9% of patients at 1 year after EBRT or LDR brachytherapy (15). In a retrospective observational study of fecal incontinence in 143 men, who had received LDR brachytherapy for localised PCa, 13.2% (21) of patients at 2 years reported that faecal incontinence was impacting their ability to participate in daily activities (35). A multivariable analysis suggested that bowel and rectal symptoms were less profound after LDR brachytherapy than after EBRT (7) (LE: 2a).

Roeloffzen et al. (31) reported a statistically significant deterioration in HRQoL in patients treated with iodine-125 LDR brachytherapy at 6 years for urinary symptoms, bowel symptoms, pain, physical functioning, and sexual activity. However, most of these changes were not clinically relevant. HRQoL scores returned to approximately baseline values at 1 year and remained stable up to 6 years after treatment. The only clinically relevant changes occurred in emotional functioning and sexual activity. Worse bowel and urinary function may play a stronger role than sexual function in predicting a patient's overall physical and emotional HRQoL (36). Contemporary treatment refinements, such as 3-D conformal or intensity-modulated radiotherapy (IMRT), may

be able to reduce the impact of EBRT on bowel symptoms, but this has not yet been shown in a multicentre setting.

Dietary intervention had no statistically significant positive impact on gastrointestinal side effects or other aspects of HRQoL in patients undergoing RT (37) (LE: 1b).

Sanda et al. showed that adjuvant androgen suppression exacerbated the adverse effects of EBRT or LDR on sexuality and vitality (15). The negative effects of adjuvant hormonal therapy have been shown in some other studies (29,38). The significant worsening of bowel function with the addition of hormones to external radiotherapy was shown at 12 and 24 months after completion of radiotherapy (39).

Among general domains, fatigue was commonly reported following EBRT. However, provided that fatigue was temporary, it did not appear to be emotionally distressing to most men (40,41). Men treated with interstitial LDR brachytherapy appeared to show only slight declines in general HRQoL (42). Physical and functional status declines have been reported in the first few months after implant, but pretreatment levels of function are regained by most men at 1 year after implant (43).

15.5 Comparison of HRQoL between treatment modalities

The limitations of all published studies assessing QoL include the lack of randomisation to treatment and therefore the presence of selection bias, which may influence outcomes. Thus, information regarding comparative outcome relies largely on results from non-randomised observational cohorts. Treatment comparison requires a long follow-up, as measures of QoL may change with time. There are very few trials that are direct comparing different treatment modalities.

Studies addressing general HRQoL issues (general physical function, role function, social function, emotional well-being, body pain, general health, or vitality/energy) have found few differences across treatments for clinically localised disease (6,44). In longitudinal studies, both surgery- and radiotherapy-treated men have reported some declines in role function and vitality/energy shortly after treatment, with surgically treated men reporting the most dysfunction (26,40). However most men recovered function by 1 year after treatment.

The presence of comorbid psychiatric conditions (i.e. prior psychiatric history, alcohol abuse, drug abuse) and the experience of pain after treatment were considered to be certain risk factors for poor general HRQoL in men after treatment for localised prostate cancer (45-47).

The PCOS was the first reported prospective study presenting treatment-specific QoL outcomes for PCa patients at 5 years after initial diagnosis (18). The cohort consisted of men with newly diagnosed localised PCa treated with RP (n = 901) or EBRT (n = 286). At 5 years after diagnosis, overall sexual function declined in both groups to approximately the same level, mostly because of a continuing decline in erectile function among EBRT patients between years 2 and 5. However, erectile dysfunction was more prevalent in the RP group (79.3% vs 63.5%, respectively). Approximately 14-16% of RP and 4% of EBRT patients were incontinent at 5 years. Bowel urgency and painful haemorrhoids were more common in the EBRT group (LE: 2a).

Madalinska et al. evaluated the side effects of RP and EBRT in 278 patients from the ERSPC study at 6 and 12 months following treatment (33). RP patients reported significantly higher incidences of urinary incontinence (39-49%) and erectile dysfunction (80-91%) than radiotherapy patients (6-7% and 41-55%, respectively). Bowel problems (urgency) affected 30-35% of the EBRT group versus 6-7% of the RP group (LE: 2a).

Downs et al. measured the impact of LDR brachytherapy alone on general HRQoL and disease-specific HRQoL compared to patients treated with RP (48). The authors studied 419 men from the CaPSURE database, whose primary treatment was LDR brachytherapy (n = 92) or RP (n = 327). Patients treated with LDR brachytherapy or RP did not differ greatly in general HRQoL after treatment. Both treatment groups showed early functional impairment in most general domains, with scores returning to or approaching baseline in most domains at 18 to 24 months after treatment. Patients treated with LDR brachytherapy had significantly higher urinary function scores at 0 to 6 months after treatment (84.5%) than patients treated with RP (63.3%). Urinary bother scores were not significantly different (67.7% vs 67.4%, respectively). Both treatment groups showed decreases in sexual function that did not return to pretreatment levels (LE: 2a).

A multicentre study that compared all three treatments (RP, EBRT, LDR brachytherapy) in a longitudinal prospective cohort was conducted by Talcott et al. (7). In 417 men, the authors assessed urinary, bowel and sexual function from before primary treatment to 24 months afterwards. Urinary incontinence increased sharply after RP, while bowel problems and urinary irritation-obstruction occurred after EBRT and LDR brachytherapy. Sexual function severely worsened immediately after surgery and then improved, while sexual function continued to decline after both radiation treatments. It has been shown that a surgical patient, who is impotent at 3 or 12 months after surgery, can expect to have a realistic hope of improvement while impotent EBRT patients probably should not. There was no change in urinary function and little change in overall bowel function after 12 months. The data showed that a patient with bowel dysfunction at 12 months after EBRT may expect modest improvement, with diverging trends for individual symptoms. Diarrhoea will continue to subside,

but there will be little change in tenesmus and rectal urgency, and episodes of rectal bleeding will become more prevalent (7) (LE: 2a).

A prospective, multicentre study of 435 patients with a longer follow-up of 36 months was reported by Pardo et al. (49). The study confirmed that there was a long-term change in adverse effects, e.g. an increase in urinary-related adverse effects after EBRT or sexual adverse effects with LDR brachytherapy, which tended to reduce any differences between treatments over time. However, these changes were only slight. In accordance with other reports, the RP-treated group showed greater deterioration in urinary incontinence and sexual function, but improved urinary irritative-obstructive results compared with the LDR brachytherapy group. In patients with urinary irritative-obstructive symptoms at baseline, improvement was observed in 64% of those treated with nerve-sparing RP. Higher bowel worsening was observed in the ERBT group, with 20% of patients reporting bowel symptoms. Relevant differences between treatment groups persisted for up to 3 years of follow-up (49) (LE: 2a).

The American College of Surgeons Oncology Group phase III Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial compared RP and LDR brachytherapy, but was closed after 2 years due to poor accrual. Crook et al. (50) recently reported the HRQoL at a mean of 5.3 years for 168 trial-eligible men, who either chose or were randomly assigned to RP or brachytherapy following a multidisciplinary educational session (50). There were no differences in bowel or hormonal domains. However, men treated with LDR brachytherapy scored slightly better in the urinary QoL domain (91.8 vs 88.1; $p = 0.02$) and sexual (52.5 vs 39.2; $p = 0.001$) domain, and in patient satisfaction (93.6 vs 76.9%; $p < 0.001$). It should be noted that treatment allocation was random in only 19% of cases (LE: 2a).

A population-based study investigated the relationship between presence of urinary, bowel or sexual dysfunction and global QoL in PCa survivors in Norway including men who did not have any active treatment. Men who had undergone RP reported more urinary incontinence (24%) than the other treatment groups, but had the lowest level of moderate or severe urinary irritative-obstructive symptoms. Men from the 'no treatment' group had the highest level of moderate or severe irritative-obstructive urinary symptoms. Men who had undergone RT reported higher levels of irritative intestinal symptoms and faecal leakage compared with the RP group and the no-treatment group. In all treatment groups, poor sexual drive and poor erectile function were common, with men treated with RP reporting the highest prevalence of poor erectile function (89%). The presence of irritative-obstructive urinary symptoms and poor sexual drive were independently associated with low global QoL in multivariate analyses. The use of medication for erectile dysfunction was not significantly associated with global QoL (14) (LE: 2b).

The QoL of a patient's spouse or partner may also be reduced as a result of their spouse or partner receiving treatment for PCa. In a prospective, multicentre, study of more than 1200 patients and 625 spouses or partners (15), distress associated with the patient's erectile dysfunction was reported by 44% of partners in the RP group, 22% of those in the EBRT group and 13% of those in the LDR brachytherapy group. After RP, urinary incontinence was observed, but urinary irritation and obstruction improved, particularly in patients with large prostates. Treatment-related symptoms were made worst by obesity, large prostate size, high prostate-specific antigen score and older age (LE: 2a).

Malcolm et al. (51) reported a single-institution study comparing the outcomes of surgery (RP, RALP), LDR brachytherapy and cryosurgical ablation of the prostate (CSAP) with a relatively short follow-up of 24 months (51). The HRQoL of patients treated with LDR brachytherapy and CSAP was associated with higher urinary function and higher bother score compared to open RP and RALP. LDR brachytherapy was associated with a higher sexual function and higher bother score compared to all other treatment modalities. Unfortunately, the study used the UCLA-PCI questionnaire, which lacks items for evaluating irritative urinary symptoms, which are often observed in patients after LDR brachytherapy (48). This may have significantly compromised the results of the HRQoL assessment (LE: 3).

In conclusion, many men treated for clinically localised PCa will experience some post-treatment problems that may impact their daily lives. Each patient therefore has to determine which side effect profile (32) is most acceptable to them when making a decision about treatment.

15.6 References

1. Leplège A, Hunt S. The problem of quality of life in medicine. JAMA 1997 Jul;278(1):47-50. http://www.ncbi.nlm.nih.gov/pubmed/9207338

2. Osoba D. Self-rating symptom checklists: a simple method for recording and evaluating symptom control in oncology. Cancer Treat Rev 1993;19 Suppl A:43-51. [no abstract available] http://www.ncbi.nlm.nih.gov/pubmed/7679319
3. Patrick DL, Erickson P. Assessing health-related quality of life for clinical decision-making. In: Quality of Life Assessment: Key Issues in the 1990s. Walker SR, Rosser RM, editors. Boston: Dordrecht Kluwer, 1993, pp. 11-64.
4. Schumacher M, Olschewski M, Schulgen G. Assessment of quality of life in clinical trials. Stat Med 1991 Dec;10(12):1915-30. http://www.ncbi.nlm.nih.gov/pubmed/1805318
5. Litwin M, Lubeck D, Henning J, et al. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: results of the CaPSURE database. J Urol 1998 Jun;159(6):1988-92. http://www.ncbi.nlm.nih.gov/pubmed/9598504
6. Eton DT, Lepore SJ. Prostate cancer and health-related quality of life: a review of the literature. Psychooncology 2002 Jul-Aug;11(4):307-26. http://www.ncbi.nlm.nih.gov/pubmed/12203744
7. Talcott JA, Manola J, Clark JA, et al. Time course and predictors of symptoms after primary prostate cancer therapy. J Clin Oncol 2003 Nov;21(21):3979-86. http://www.ncbi.nlm.nih.gov/pubmed/14581420
8. Clark JA, Talcott JA. Symptom indexes to assess outcomes of treatment for early prostate cancer. Med Care 2001 Oct;39(10):1118-30. http://www.ncbi.nlm.nih.gov/pubmed/11567174
9. Joly F, Brune D, Couette JE, et al. Health-related quality of life and sequelae in patients treated with brachytherapy and external beam irradiation for localized prostate cancer. Ann Oncol 1998 Jul;9(7):751-7. http://www.ncbi.nlm.nih.gov/pubmed/9739442
10. van den Bergh RC, Essink-Bot ML, Roobol MJ, et al. Anxiety and distress during active surveillance for early prostate cancer. Cancer 2009 Sep 1;115(17):3868-78. http://www.ncbi.nlm.nih.gov/pubmed/19637245
11. van den Bergh RC, Essink-Bot ML, Roobol MJ, et al. Do anxiety and distress increase during active surveillance for low risk prostate cancer? J Urol 2010 May;183(5):1786-91. http://www.ncbi.nlm.nih.gov/pubmed/20299064
12. Holmberg L, Bill-Axelson A, Helgesen F, et al. Scandinavian Prostatic Cancer Group Study Number 4. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 2002 Sep 12;347(11):781-9. http://www.ncbi.nlm.nih.gov/pubmed/12226148
13. Bellizzi KM, Latini DM, Cowan JE, et al. Fear of recurrence, symptom burden, and health-related quality of life in men with prostate cancer. Urology 2008 Dec;72(6):1269-73. http://www.ncbi.nlm.nih.gov/pubmed/18342930
14. Kyrdalen AE, Dahl AA, Hernes E et al. A national study of adverse effects and global quality of life among candidates for curative treatment for prostate cancer. BJU Int 2012 Jun 6 doi: 10.1111/j.1464-410X.2012.11198.x. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/22672151
15. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008 Mar;358(12):1250-61. http://www.ncbi.nlm.nih.gov/pubmed/18354103
16. Gacci M, Simonato A, Masieri L, et al. Urinary and sexual outcomes in long-term (5+ years) prostate cancer disease free survivors after radical prostatectomy. Health Qual Life Outcomes 2009 Nov;7:94. http://www.ncbi.nlm.nih.gov/pubmed/19912640
17. Chen RC, Clark JA, Talcott JA. Individualizing quality-of-life outcomes reporting: how localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel, and sexual function. J Clin Oncol 2009 Aug;27(24):3916-22. http://www.ncbi.nlm.nih.gov/pubmed/19620493
18. Potosky AL, Legler J, Albertsen PC, et al. Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. J Natl Cancer Inst 2000 Oct;92(19):1582-92. http://www.ncbi.nlm.nih.gov/pubmed/11018094
19. Ku J, Krahn M, Trachtenberg J, et al. Changes in health utilities and health-related quality of life over 12 months following radical prostatectomy. Can Urol Assoc J 2009 Dec;3(6):445-52. http://www.ncbi.nlm.nih.gov/pubmed/20019969

20. Litwin MS, Melmed GY, Nakazon T. Life after radical prostatectomy: a longitudinal study. J Urol 2001 Aug;166(2):587-92.
http://www.ncbi.nlm.nih.gov/pubmed/11458073
21. Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. JAMA 2000 Jan;283(3): 354-60.
http://www.ncbi.nlm.nih.gov/pubmed/10647798
22. Smith DS, Carvalhal GF, Schneider K, et al. Quality-of-life outcomes for men with prostate carcinoma detected by screening. Cancer 2000 Mar 15;88(6):1454-63.
http://www.ncbi.nlm.nih.gov/pubmed/10717630
23. Abel EJ, Masterson TA, Warner JN, et al. Nerve-sparing prostatectomy and urinary function: a prospective analysis using validated quality-of-life measures. Urology 2009 Jun;73(6):1336-40.
http://www.ncbi.nlm.nih.gov/pubmed/19362347
24. Nandipati KC, Raina R, Agarwal A, et al. Nerve-sparing surgery significantly affects long-term continence after radical prostatectomy. Urology 2007 Dec;70(6):1127-30.
http://www.ncbi.nlm.nih.gov/pubmed/18158032
25. Coelho RF, Chauhan S, Palmer KJ, et al. Robotic-assisted radical prostatectomy: a review of current outcomes. BJU Int 2009 Nov;104(10):1428-35.
http://www.ncbi.nlm.nih.gov/pubmed/19804427
26. Lubeck DP, Litwin MS, Henning JM, et al. Changes in health-related quality of life in the first year after treatment for prostate cancer: results from CaPSURE. Urology 1999 Jan;53(1):180-6.
http://www.ncbi.nlm.nih.gov/pubmed/9886609
27. Bianco FJ Jr, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology 2005 Nov;66(5 Suppl):83-94.
http://www.ncbi.nlm.nih.gov/pubmed/16194712
28. Patel VR, Sivaraman A, Coelho RF, et al. Pentafecta: a new concept for reporting outcomes of robot-assisted laparoscopic radical prostatectomy. Eur Urol 2011 May;59(5):702-7.
http://www.ncbi.nlm.nih.gov/pubmed/21296482
29. Wei JT, Dunn RL, Sandler HM, et al. Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer. J Clin Oncol 2002 Jan;20(2):557-66.
http://www.ncbi.nlm.nih.gov/pubmed/11786586
30. Roeloffzen EM, Hinnen KA, Battermann JJ, et al. The impact of acute urinary retention after iodine-125 prostate brachytherapy on health-related quality of life. Int J Radiat Oncol Biol Phys 2010 Aug 1;77(5):1322-8.
http://www.ncbi.nlm.nih.gov/pubmed/19939578
31. Roeloffzen EM, Lips IM, van Gellekom MP, et al. Health-related quality of life up to six years after (125)I brachytherapy for early-stage prostate cancer. Int J Radiat Oncol Biol Phys 2010 Mar;76(4):1054-60.
http://www.ncbi.nlm.nih.gov/pubmed/20097486
32. Dandapani SV, Sanda MG. Measuring health-related quality of life consequences from primary treatment for early-stage prostate cancer. Semin Radiat Oncol 2008 Jan;18(1):67-72.
http://www.ncbi.nlm.nih.gov/pubmed/18082590
33. Madalinska JB, Essink-Bot ML, de Koning HJ, et al. Health-related quality-of-life effects of radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed localized prostate cancer. J Clin Oncol 2001 Mar;19(6):1619-28.
http://www.ncbi.nlm.nih.gov/pubmed/11250990
34. Miller DC, Sanda MG, Dunn RL, et al. Long-term outcomes among localized prostate cancer survivors: health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy. J Clin Oncol 2005 Apr;23(12):2772-80.
http://www.ncbi.nlm.nih.gov/pubmed/15837992
35. Lamb MN, Trabinino L, Hackford A. Patients' perspectives on fecal incontinence after brachytherapy for localized prostate cancer. Dis Colon Rectum 2011 May;54(5):615-21.
http://www.ncbi.nlm.nih.gov/pubmed/21471764
36. Steenland K, Goodman M, Liff J, et al. Quality of life among men with prostate cancer in rural Georgia. Urology 2011 Apr;77(4):927-33.
http://www.ncbi.nlm.nih.gov/pubmed/21334050
37. Petterson A, Johansson B, Persson C et al Effects of a dietary intervention on acute gastrointestinal side effects and other aspects of health-related quality of life: a randomized controlled trial in prostate cancer patients undergoing radiotherapy. Radiother Oncol 2012 Jun; 103(3):333-40.
http://www.ncbi.nlm.nih.gov/pubmed/22633817

38. Bestmann B, Kollakowski T, Weissbach L. [Quality of life after prostate cancer in members of support groups: first results of the HAROW retro study.] Urologe A 2011 Mar;50(3):333-9. [Article in German] http://www.ncbi.nlm.nih.gov/pubmed/21290094
39. Brassel SA, Elsamanoudi SI, Cullen J et al. Health-related quality of life for men with prostate cancer-an evaluation of outcomes 12-24 months after treatment. Urol Oncol 2012 May 17. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/22608541
40. Beard CJ, Propert KJ, Rieker PP, et al. Complications after treatment with external-beam irradiation in early-stage prostate cancer patients: a prospective multiinstitutional outcomes study. J Clin Oncol 1997 Jan;15(1):223-9. http://www.ncbi.nlm.nih.gov/pubmed/8996146
41. Monga U, Jaweed M, Kerrigan AJ, et al. Neuromuscular fatigue in prostate cancer patients undergoing radiation therapy. Arch Phys Med Rehabil 1997 Sep;78(9):961-6. http://www.ncbi.nlm.nih.gov/pubmed/9305269
42. Penson DF, Litwin MS, Aaronson NK. Health related quality of life in men with prostate cancer. J Urol 2003 May;169(5):1653-61. http://www.ncbi.nlm.nih.gov/pubmed/12686803
43. Lee WR, McQuellon RP, Harris-Henderson K, et al. A preliminary analysis of health-related quality of life in the first year after permanent source interstitial brachytherapy (PIB) for clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 2000 Jan;46(1):77-81. http://www.ncbi.nlm.nih.gov/pubmed/10656376
44. Litwin MS, Hays RD, Fink A, et al. Quality-of-life outcomes in men treated for localized prostate cancer. JAMA 1995 Jan;273(2):129-35. http://www.ncbi.nlm.nih.gov/pubmed/7799493
45. Schag CA, Ganz PA, Wing DS, et al. Quality of life in adult survivors of lung, colon and prostate cancer. Qual Life Res 1994 Apr;3(2):127-41. http://www.ncbi.nlm.nih.gov/pubmed/8044158
46. Borghede G, Karlsson J, Sullivan M. Quality of life in patients with prostatic cancer: results from a Swedish population study. J Urol 1997 Oct;158(4):1477-85; discussion 1486. http://www.ncbi.nlm.nih.gov/pubmed/9302147
47. Heim HM, Oei TP. Comparison of prostate cancer patients with and without pain. Pain 1993 May;53(2):159-62. http://www.ncbi.nlm.nih.gov/pubmed/8336985
48. Downs TM, Sadetsky N, Pasta DJ, et al. Health related quality of life patterns in patients treated with interstitial prostate brachytherapy for localized prostate cancer--data from CaPSURE. J Urol 2003 Nov;170(5):1822-7. http://www.ncbi.nlm.nih.gov/pubmed/14532784
49. Pardo Y, Guedea F, Aguiló F, et al. Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. J Clin Oncol 2010 Nov;28(31):4687-96. http://www.ncbi.nlm.nih.gov/pubmed/20921463
50. Crook JM, Gomez-Iturriaga A, Wallace K, et al. Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial. J Clin Oncol 2011 Feb 1;29(4):362-8. http://www.ncbi.nlm.nih.gov/pubmed/21149658
51. Malcolm JB, Fabrizio MD, Barone BB, et al. Quality of life after open or robotic prostatectomy, cryoablation or brachytherapy for localized prostate cancer. J Urol 2010 May;183(5):1822-8. http://www.ncbi.nlm.nih.gov/pubmed/20303100

16. SUMMARY OF GUIDELINES ON PRIMARY TREATMENT OF PCA

Stage	Treatment	Comment	GR
T1a	Watchful waiting	Standard treatment for Gleason score ≤ 6 and 7 adenocarcinomas and < 10-year life expectancy.	B
	Active surveillance	In patients with > 10-year life expectancy, re-staging with TRUS and biopsy is recommended.	B
	Radical prostatectomy	Optional in younger patients with a long life expectancy, especially for Gleason score ≥ 7 adenocarcinomas.	B
	Radiotherapy	Optional in younger patients with a long life expectancy, in particular in poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation.	B
	Hormonal	Not an option.	A
	Combination	Not an option.	C
T1b-T2b	Active surveillance	Treatment option in patients with cT1c-cT2a, PSA < 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 biopsies positive, ≤ 50% cancer involvement of each biopsy.	B
		Patients with a life expectancy < 10 years.	
		Patients with a life expectancy > 10 years once they are informed about the lack of survival data beyond 10 years.	
		Patients who do not accept treatment-related complications.	
T1a-T2c	Radical prostatectomy	Optional in patients with pT1a PCa. Standard treatment for patients with a life expectancy > 10 years who accept treatment-related complications.	A
	Radiotherapy	Patients with a life expectancy > 10 years who accept treatment-related complications.	B
		Patients with contraindications for surgery.	
		Unfit patients with 5-10 years of life expectancy and poorly differentiated tumours (combination therapy is recommended; see below).	
	Brachytherapy	Low-dose rate brachytherapy can be considered for low risk PCa patients with a prostate volume ≤ 50 mL and an IPSS ≤ 12.	B
	Hormonal	Symptomatic patients, who need palliation of symptoms, unfit for curative treatment.	C
		Anti-androgens are associated with a poorer outcome compared to 'active surveillance' and are not recommended.	A
	Combination	For high-risk patients, neoadjuvant hormonal treatment and concomitant hormonal therapy plus radiotherapy results in increased overall survival.	A

T3-T4	Watchful waiting	Option in asymptomatic patients with T3, well-differentiated and moderately-differentiated tumours, and a life expectancy < 10 years who are unfit for local treatment.	C
	Radical prostatectomy	Optional for selected patients with T3a, PSA < 20 ng/mL, biopsy Gleason score ≤ 8 and a life expectancy > 10 years.	C
		Patients have to be informed that RP is associated with an increased risk of positive surgical margins, unfavourable histology and positive lymph nodes and that, therefore, adjuvant or salvage therapy such as radiation therapy or androgen deprivation might be indicated.	
	Radiotherapy	T3 with > 5-10 years of life expectancy. Dose escalation of > 74 Gy seems to be of benefit. A combination with hormonal therapy can be recommended.	A
	Hormonal	Symptomatic patients, extensive T3-T4, high PSA level (> 25-50 ng/mL), PSA-Doubling Time (DT) < 1 year.	A
		Patient-driven, unfit patients.	
		Hormone monotherapy is not an option for patients who are fit enough for radiotherapy.	
	Combination	Overall survival is improved by concomitant and adjuvant hormonal therapy (3 years) combined with external beam radiation.	A
		NHT plus radical prostatectomy: no indication.	B
N+, M0	Watchful waiting	Asymptomatic patients. Patient-driven (PSA < 20-50 ng/mL), PSA DT > 12 months. Requires very close follow-up.	B
	Radical prostatectomy	Optional for selected patients with a life expectancy of > 10 years as part of a multimodal treatment approach.	C
	Radiotherapy	Optional in selected patients with a life expectancy of > 10 years, combination therapy with adjuvant androgen deprivation for 3 years is mandatory.	C
	Hormonal	Standard adjuvant therapy in more than 2 positive nodes to radiation therapy or radical prostatectomy as primary local therapy. Hormonal therapy should only be used as monotherapy in patients who are unfit for any type of local therapy.	A
	Combination	No standard option. Patient-driven.	B
M+	Watchful waiting	No standard option. May have worse survival/more complications than with immediate hormonal therapy. Requires very close follow-up.	B
	Radical prostatectomy	Not a standard option.	C
	Radiotherapy	Not an option for curative intent; therapeutic option in combination with androgen deprivation for treatment of local cancer-derived symptoms.	C
	Hormonal	Standard option. Mandatory in symptomatic patients.	A

DT = doubling time; NHT = neoadjuvant hormonal treatment; IPSS = International Prostatic Symptom Score; PSA = prostatespecific antigen; TRUS = transrectal ultrasound; TURP =transurethral resection of the prostate

17. FOLLOW-UP: AFTER TREATMENT WITH CURATIVE INTENT

17.1 Definition

Curative treatment is defined as radical prostatectomy or radiotherapy, either by external beam radiation or an interstitial technique, or any combination of these. Alternative treatment options that are not fully established,

such as HIFU, do not have a well-defined, validated PSA-cut-point to define biochemical failure but do generally follow the outlines given below.

17.2 Why follow-up?

The first question to be answered is: 'If failure after curative treatment is so common, are follow-up efforts worthwhile?' The answer to this question is definitely 'yes'. Recurrences will occur in a substantial number of patients who received treatment with intent to cure at various time points after the primary therapy.

The second question to be answered is: 'What is the reason for follow-up?' Reasons may vary depending on the treatment given, patient age, co-morbidity and the patient's own wishes. In general, patients who receive curative therapy may be followed-up for any of the following reasons:

- good responsible patient care;
- possibility of second-line treatment with curative intent;
- possibility of early hormonal therapy after failure;
- as part of a study protocol.

Chapter 18 discusses treatment options after failure of primary therapy.

17.3 How to follow-up?

The procedures indicated at follow-up visits vary depending on the clinical situation. The examinations discussed below are routinely used for the detection of PCa progression or residual disease. The PSA level, and eventually DRE, are the only tests that need to be carried out routinely. A disease-specific history should be mandatory at every follow-up visit and should include psychological aspects, signs of disease progression, and treatment-related complications. The examinations used for the evaluation of treatment-related complications must be individualised and are beyond the scope of these guidelines. The examinations used most often for cancer-related follow-up after curative surgery or radiation treatment are discussed below.

*17.3.1 **PSA monitoring***

The measurement of PSA level is a cornerstone in the follow-up after curative treatment. There is a difference in what can be expected after radical prostatectomy and radiotherapy, but PSA recurrence nearly always precedes clinical recurrence after either treatment, in some cases by many years (1-5). It is recommended that the finding of a single, elevated, serum PSA level should be re-confirmed before second-line therapy is started solely based on the PSA elevation.

*17.3.2 **Definition of PSA progression***

The level of PSA at which to define treatment failure differs between radical prostatectomy cases and radiation treated cases. Following radical retropubic prostatectomy, two consecutive values of 0.2 ng/mL or greater appear to represent an international consensus defining recurrent cancer (6,7). Other authors have argued for an even higher cut-off of 0.4 ng/mL to better define patients with a high risk for clinical progression (5). It has been shown that patients with a PSA level between 0.1 ng/mL and 0.2 ng/mL after radical prostatectomy had neither clinical nor biochemical disease progression (8). Therefore, the use of an ultra-sensitive PSA assay is not justified for routine follow-up after radical prostatectomy (4). If ongoing randomised trials show that early adjuvant treatment after radical prostatectomy (given before PSA reaches > 0.2 ng/mL) improves survival, this issue should be reconsidered.

Following radiation therapy, until recently, the definition of biochemical relapse was three consecutive increases according to the recommendation of ASTRO from 1996 (9). At the 2006 RTOG-ASTRO Consensus conference a new definition of radiation failure was established with as the main aim to establish a better correlation between the definition and clinical outcome. The new definition of radiation failure is a rise of 2 ng/mL above the post-treatment PSA-nadir (lowest value) (10). This definition is applicable for patients treated with or without hormonal therapy.

After HIFU or cryotherapy, a variety of definitions for PSA-relapse have been used (11). Most of these are based on a cut-off of around 1 ng/mL, eventually combined with a negative post-treatment biopsy. As yet, none of these end-points have been validated against clinical progression or survival and therefore it is not possible to give firm recommendations on the definition of biochemical failure.

*17.3.3 **PSA monitoring after radical prostatectomy***

PSA is expected to be undetectable within 6 weeks after a successful radical prostatectomy (12). A persistently elevated PSA level means that PSA-producing tissue remains in the body. In patients treated with radical prostatectomy, this is generally thought to be residual cancer due to either micrometastases that were not detected or undetectable beforehand, or residual disease in the pelvis possibly due to positive surgical margins.

A rapidly increasing PSA level (high PSA velocity, short PSA doubling time) indicates distant metastases, while a later and slowly increasing concentration of PSA is most likely to indicate local disease recurrence. The time to PSA recurrence and tumour differentiation are also important predictive factors distinguishing between local and systemic recurrence (13,14). Both local treatment failure and distant metastases have been shown to occur with undetectable PSA levels. This is very rare and occurs almost only in patients with unfavourable pathology (undifferentiated tumours) (15,16).

This means that, in patients with a relatively favourable pathology (< pT3, pN0, Gleason score < 8), PSA measurement, together with the disease-specific history, could stand as the single test in follow-up after radical prostatectomy.

17.3.4 ***PSA monitoring after radiation therapy***

The PSA level falls slowly after radiotherapy compared with radical prostatectomy. The optimal cut-off value for a favourable PSA nadir after radiotherapy is somewhat controversial. Achieving a PSA nadir of less than 0.5 ng/mL seems to be associated with a favourable outcome (17). The interval before reaching the nadir PSA may be very long and can sometimes take up to 3 years or more. A PSA rising more than 2 ng/mL above the nadir PSA is the current definition of biochemical failure after radiotherapy (10). Also, after radiotherapy, the PSA doubling time has been shown to correlate to the site of recurrence; patients with local recurrence had a doubling time of 13 months compared to 3 months for those with distant failure (18).

17.3.5 ***Digital rectal examination (DRE)***

DRE is performed to assess whether or not there is any sign of local disease recurrence. It is very difficult to interpret the findings of DRE after curative therapy, especially after radiotherapy. A newly detected nodule should raise the suspicion of local disease recurrence.

As mentioned previously, a local disease recurrence after curative treatment is possible without a concomitant rise in PSA level (15,16). However, this has only been proven in patients with unfavourable pathology, i.e. those with undifferentiated tumours. Thus, PSA measurement and DRE comprise the most useful combination of tests as first-line examination in follow-up after radiotherapy or radical prostatectomy, but PSA measurement may well be the only test in cases with favourable pathology (19).

17.3.6 ***Transrectal ultrasonography (TRUS) and biopsy***

TRUS and biopsy have no place in the routine follow-up of asymptomatic patients and nowadays only rarely after biochemical failure. TRUS cannot stand alone as a diagnostic tool, but must usually be combined with biopsy to establish the presence of local disease recurrence. The purpose of the investigation is to confirm a histological diagnosis of local disease recurrence. It is only warranted if the finding of a local recurrence affects the treatment decision (see Section 16 for a more detailed discussion).

17.3.7 ***Bone scintigraphy***

The purpose of bone scintigraphy is to detect skeletal metastases. It is not recommended for the routine follow-up of asymptomatic patients, but may be indicated in individuals with elevated PSA levels for whom the findings will affect the treatment decision. It is also indicated in patients with symptoms arising from the skeleton, since metastatic disease may occur even if PSA is undetectable (15,16).

17.3.8 ***Computed tomography (CT) or magnetic resonance imaging (MRI)***

CT or MRI have no place in the routine follow-up of asymptomatic patients. They may be used selectively in the evaluation after biochemical failure before treatment decisions are made (see Chapter 18).

17.4 When to follow-up?

Most patients who fail treatment for PCa do so early, even if failure only becomes clinically obvious after years. The patient should therefore be followed-up more closely during the first years after treatment when the risk of failure is highest. PSA measurement, disease-specific history and DRE are recommended at the following intervals: 3, 6 and 12 months postoperatively, every 6 months thereafter until 3 years, and then annually. The purpose of the first clinic visit is mainly to detect treatment-related complications and to assist patients in coping with the new situation. Tumour or patient characteristics may allow alterations to this schedule. For example, patients with poorly differentiated and locally advanced tumours or with positive margins may be followed-up more closely than those with a well-differentiated, intracapsular or specimenconfined tumour. Obviously, advanced age or associated co-morbidity may make further follow-up in asymptomatic patients superfluous.

17.5 Guidelines for follow-up after treatment with curative intent

Recommendations	GR
In asymptomatic patients, a disease-specific history and a serum PSA measurement supplemented by DRE are the recommended tests for routine follow-up. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.	B
After radical prostatectomy, a serum PSA level of more than 0.2 ng/mL can be associated with residual or recurrent disease.	B
After radiation therapy, a rising PSA level over 2 ng/mL above the nadir PSA, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease.	B
Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence.	B
Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the treatment plan. In most cases TRUS and biopsy are not necessary before second-line therapy.	B
Metastasis may be detected by pelvic CT/MRI or bone scan. In asymptomatic patients, these examinations may be omitted if the serum PSA level is less than 20 ng/mL but data on this topic are sparse.	C
Routine bone scans and other imaging studies are not recommended in asymptomatic patients. If a patient has bone pain, a bone scan should be considered irrespective of the serum PSA level.	B

17.6 References

1. Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancerspecific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Urol Clin North Am 2001 Aug;28(3)555-65. http://www.ncbi.nlm.nih.gov/pubmed/11590814
2. Rosser CJ, Chichakli R, Levy LB, et al. Biochemical disease-free survival in men younger than 60 years with prostate cancer treated with external beam radiation. J Urol 2002 Aug;168(2):536-41. http://www.ncbi.nlm.nih.gov/pubmed/12131304
3. Horwitz EM, Thames HD, Kuban DA, et al. Definitions of biochemical failure that best predict clinical failure in patients with prostate cancer treated with external beam radiation alone: a multi-institutional pooled analysis. J Urol 2005 Mar;173(3):797-802. http://www.ncbi.nlm.nih.gov/pubmed/15711272
4. Taylor JA III, Koff SG, Dauser DA, et al. The relationship of ultrasensitive measurements of prostatespecific antigen levels to prostate cancer recurrence after radical prostatectomy. BJU Int 2006 Sep;98(3):540-3. http://www.ncbi.nlm.nih.gov/pubmed/16925750
5. Stephenson AJ, Kattan MW, Eastham JA, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. J Clin Oncol 2006 Aug;24(24):3973-8. http://www.ncbi.nlm.nih.gov/pubmed/16921049
6. Boccon-Gibod L, Djavan WB, Hammerer P, et al. Management of prostate-specific antigen relapse in prostate cancer: a European Consensus. Int J Clin Pract 2004 Apr;58(4):382-90. http://www.ncbi.nlm.nih.gov/pubmed/15161124
7. Moul JW. Prostate specific antigen only progression of prostate cancer. J Urol 2000 Jun;163(6): 1632-42. http://www.ncbi.nlm.nih.gov/pubmed/10799151
8. Schild SE, Wong WW, Novicki DE, et al. Detection of residual prostate cancer after radical prostatectomy with the Abbott Imx PSA assay. Urology 1996 Jun;47(6):878-81. http://www.ncbi.nlm.nih.gov/pubmed/8677580
9. American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statement: guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys 1997 Mar;37(5):1035-41. http://www.ncbi.nlm.nih.gov/pubmed/9169810
10. Roach III M, Hanks G, Thames jr H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix consensus conference. Int J Radiat Oncol Biol Phys 2006 Jul;65(4):965-74. http://www.ncbi.nlm.nih.gov/pubmed/16798415

11. Aus G. Current status of HIFU and cryotherapy in prostate cancer - a review. Eur Urol 2006 Nov;50(5): 927-34.
http://www.ncbi.nlm.nih.gov/pubmed/16971038
12. Stamey TA, Kabalin JN, McNeal JE, et al. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. J Urol 1989 May;141(5): 1076-83.
http://www.ncbi.nlm.nih.gov/pubmed/2468795
13. Partin AW, Pearson JD, Landis PK, et al. Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. Urology 1994 May;43(5):649-59.
http://www.ncbi.nlm.nih.gov/pubmed/7513108
14. Trapasso JG, deKernion JB, Smith RB, et al. The incidence and significance of detectable levels of serum prostate specific antigen after radical prostatectomy. J Urol 1994 Nov;152(5 Pt 2):1821-5.
http://www.ncbi.nlm.nih.gov/pubmed/7523728
15. Oefelein MG, Smith N, Carter M, et al. The incidence of prostate cancer progression with undetectable serum prostate specific antigen in a series of 394 radical prostatectomies. J Urol 1995 Dec;154(6):2128-31.
http://www.ncbi.nlm.nih.gov/pubmed/7500474
16. Leibman BD, Dilliouglugil O, Wheeler TM, et al. Distant metastasis after radical prostatectomy in patients without an elevated serum prostate specific antigen level. Cancer 1995 Dec;76(12):2530-4.
http://www.ncbi.nlm.nih.gov/pubmed/8625081
17. Ray ME, Thames HD, Levy LB, et al. PSA nadir predicts biochemical and distant failure after external beam radiotherapy for prostate cancer: a multi-institutional analysis. Int J Radiat Oncol Biol Phys 2006 Mar;64(4):1140-50.
http://www.ncbi.nlm.nih.gov/pubmed/16198506
18. Hancock SL, Cox RS, Bagshaw MA. Prostate specific antigen after radiotherapy for prostate cancer: a reevaluation of long-term biochemical control and the kinetics of recurrence in patients treated at Stanford University. J Urol 1995 Oct;154(4):1412-17.
http://www.ncbi.nlm.nih.gov/pubmed/7544843
19. Chaplin BM, Wildhagen MF, Schroder FH, et al. Digital rectal examination is no longer necessary in the routine follow-up of men with undetectable prostate specific antigen after radical prostatectomy: the implications for follow-up. Eur Urol 2005 Aug;48(6):906-10.
http://www.ncbi.nlm.nih.gov/pubmed/16126322

18. FOLLOW-UP AFTER HORMONAL TREATMENT

18.1 Introduction

A large proportion of patients treated with hormonal therapy have either metastatic or locally advanced tumours at diagnosis. This will affect the scheme of follow-up because biochemical failure is often associated with rapid symptomatic progression.

18.2 Purpose of follow-up

The main objectives of following-up these patients are to:

- monitor the response to treatment;
- ensure compliance with treatment;
- detect potential complications of endocrine therapy;
- guide the modalities of palliative symptomatic treatment at the time of CRPC.

It is important to be clear about which complementary investigations are helpful at different stages of the disease to avoid unnecessary patient examinations and excessive economic cost. In addition, strict recommendations for follow-up procedures are only useful if effective therapeutic strategies are available in cases of disease progression. To date, the issue of early versus late initiation of non-hormonal treatment in CRPC has still not been resolved, so follow-up should be performed on an individual basis. Based on current knowledge, it is not possible to formulate level 1 evidence guidelines for follow-up procedures following hormonal therapy.

18.3 Methods of follow-up

18.3.1 ***Prostate-specific antigen monitoring***

Prostate-specific antigen is a good marker for following the course of metastatic PCa. The initial PSA level can be a reflection of the extent of metastatic disease, although some poorly differentiated tumours do not secrete PSA. In recent decades, the PSA value has been used to predict the duration of response to endocrine treatment, based on either the initial pre-treatment value or the PSA decrease during the first 3-6 months. However, the prognostic value of the pre-treatment PSA value is variably assessed in the literature and should not be used alone to predict the duration of treatment response (1).

Treatment response may be assessed using the change in serum PSA level as a surrogate endpoint for survival in patients with newly diagnosed metastatic PCa after hormonal treatment has been initiated. Patients with the lowest absolute value of serum PSA (< 0.2 ng/mL) have been shown to have the best survival compared to patients with a value of 0.2-4.0 ng/mL or > 4.0 ng/mL (2). Similar results have been seen in other studies of locally advanced and metastatic PCa (3-5). The PSA response has been shown to be equally important in patients treated with hormonal therapy, following a rising PSA after treatments with curative intent (radical prostatectomy, radiation therapy). Patients with the best response also had the best survival (6,7).

Despite its usefulness in determining treatment response in individual patients, the role of PSA as a surrogate end-point in clinical trials is more controversial (8). After the initial phase of response to endocrine treatment, patients should be regularly monitored to detect and treat any complications of endocrine escape. Clinical disease progression occurs after a median interval of about 12-18 months of treatment in patients with stage M1 disease. It is well established that regular PSA control in asymptomatic patients allows the earlier detection of biochemical escape because a rise in PSA level usually precedes the onset of clinical symptoms by several months. However, it must be stressed that the PSA level is not the absolute marker of escape and should not be used alone as a follow-up test. Clinical disease progression (usually bone pain) with normal PSA levels has been reported to occur.

18.3.2 ***Creatinine, haemoglobin and liver function monitoring***

Creatinine monitoring has some value because it can detect upper urinary tract obstruction in cases of advanced cancer, which might need to be relieved by, for example, percutaneous nephrostomy or a JJ-stent.

Haemoglobin and liver function tests may suggest disease progression and/or toxicity of hormonal treatment, which can lead to interruption of hormonal treatment (i.e. liver toxicity from non-steroidal antiandrogens). It is important to remember that haemoglobin levels will decrease by about 20% with androgen deprivation (9).

Alkaline phosphatase and its bone-specific isoenzymes have the advantage of not being directly influenced by hormonal therapy compared with PSA. These markers may be used to monitor patients with stage M1b disease. It should be remembered that increases in serum alkaline phosphatase may be due to androgen-induced osteoporosis (10), and in this context, it may be helpful to determine the level of bone-specific alkaline phosphatase.

18.3.3 ***Bone scan, ultrasound and chest X-ray***

In routine practice, asymptomatic patients with a stable PSA level should not undergo a bone scan at regular intervals, because disease progression is more reliably detected by PSA monitoring, which also has a lower cost (11,12).

Moreover, it is also sometimes difficult to interpret bone scans. Thus, in an asymptomatic patient, the therapeutic approach is not modified by the appearance of a new site of uptake or deterioration of pre-existing lesions. Recently, the PCWG2 has clarified the definition of bone scan progression as the appearance of at least two new lesions (13).

Clinical or laboratory suspicion of disease progression indicates the need for a chest X-ray or renal and hepatic ultrasound. Imaging modalities must also be guided by symptoms. However, these examinations are not recommended for routine use in asymptomatic patients. In CRPC disease, follow-up examinations should be individualised with the aim of maintaining the patient's quality of life.

During long-term ADT, it may be necessary to introduce regular measurement of BMD (LE: 3), based on the initial T-score (14). Bone mineral density should be measured every 2 years if the initial T-score < 1.0, or every year if the T-score is between 1.0 and 2.5, in the absence of associated risk factors (LE: 4). Otherwise, active protective bone treatment should have started at the initiation of ADT (see Chapter 12).

18.4 Testosterone monitoring

Most PCa patients receiving LHRH analogues will achieve serum testosterone values at or below the castration level (< 20 ng/dL). However, about 13-38% of patients fail to achieve this therapeutic goal, while 2-17% of patients do not achieve a serum testosterone level below 50 ng/dL (15-17). Furthermore, up to 24% of men treated with LHRH analogues may experience testosterone surges (testosterone > 50 ng/dL) during long-term

treatment upon re-administration of the agonist drug, which is described as the 'acute on-chronic effect' or 'breakthrough responses' (16,18).

In view of these findings, the measurement of serum testosterone levels, as well as serum PSA levels, should be considered as part of clinical practice for men on LHRH therapy. The timing of testosterone measurements is not clearly defined. The first evaluation of testosterone level can be recommended at 1 month after initiating LHRH therapy to check the nadir testosterone level achieved before re-administration of the agonist drug. A 6-month testosterone level assessment may be performed to evaluate the effectiveness of treatment and to ensure the castration level is being maintained. If it is not being maintained, switching to another LHRH agent or surgical orchiectomy can be attempted. In patients with a rising PSA and/or clinical signs of progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

18.5 Monitoring of metabolic complications

Androgen deprivation therapy is beneficial in patients with prostate cancer, but has a greater range of complications than might be expected (see Chapter 12). The most common side-effects of low testosterone levels include hot flashes, lack of libido, erectile dysfunction, gynaecomastia and loss of bone mineral density. In addition, recent studies have suggested that men with low testosterone levels have a higher prevalence of metabolic complications (19), including insulin resistance, arterial stiffness, diabetes and metabolic syndrome. Research has shown that the metabolic syndrome is present in more than 50% of men undergoing long-term ADT, predisposing them to a higher cardiovascular risk (20). Men with metabolic syndrome are almost three times more likely to die of coronary heart disease and other cardiovascular diseases (21), which have now become the most common cause of death in prostate cancer patients, even exceeding prostate cancer mortality (22).

In view of these findings, a cardiology consultation may be beneficial in men with a history of cardiovascular disease and men older than 65 years prior to starting ADT. All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and then every 3 months [LE: 3]). In selected cases, glucose tolerance testing may be required. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. Patients on ADT should be given advice on modifying their lifestyle (e.g. diet, exercise, smoking cessation, etc.) and should be treated for any existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension (23,24). The patient's GP or family physician should probably be more involved in those patients at risk of cardiovascular disease, including monitoring of fasting glucose, lipids profile and blood pressure, which is recommended in all patients receiving long-term ADT. Furthermore, the risk-to-benefit ratio of ADT must be considered in patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT (19,25).

Monitoring bone health is also important, particularly serum levels of Vitamin D and calcium. If needed, supplements should be given so that the patient receives a daily intake of at least 1200 mg/day of calcium and 1000 UI of vitamin D. Preventive therapy with biphosphonates or denosumab should be considered in patients who have an initial T-score of less than -2.5 on dual-energy X-ray absorptiometry (DEXA), which is the definition of osteoporosis. However, optimal bone monitoring using DEXA is still controversial and should be prospectively evaluated. It is currently suggested that bone monitoring should be performed every 2 years after initiation of castration, provided there are no other risk factors (26), and every year if there are risk factors (27,28).

18.6 When to follow-up

After initiation of hormonal treatment, it is recommended that patients be followed-up at 3 and 6 months. These guidelines must be individualised, and each patient should be told to contact his physician in the event of troublesome symptoms.

18.6.1 ***Stage M0 patients***

If there is a good treatment response, i.e. symptomatic improvement, good psychological coping, good treatment compliance, and a serum PSA level of less than 4 ng/mL, follow-up visits are scheduled every 6 months.

18.6.2 ***Stage M1 patients***

If there is a good treatment response, i.e. good symptomatic improvement, good psychological coping, good treatment compliance, and a serum PSA level of less than 4 ng/mL, follow-up is scheduled every 3 to 6 months.

18.6.3 ***Castration-refractory PCa***

Patients whose disease progresses, or who do not respond according to the criteria mentioned above, warrant an individualised follow-up scheme.

18.7 Guidelines for follow-up after hormonal treatment

Recommendation	GR
Patients should be evaluated at 3 and 6 months after the initiation of treatment.	
As a minimum, tests should include serum PSA measurement, digital rectal examination (DRE), serum testosterone, and careful evaluation of symptoms in order to assess the treatment response and the side-effects of the treatments given.	B
If patients undergo intermittent androgen deprivation, PSA and testosterone should be monitored in 3-month intervals during the treatment pause.	C
Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.	C
In patients with stage M0 disease with a good treatment response, follow-up is scheduled every 6 months, and should include as a minimum a disease-specific history, DRE and serum PSA determination.	C
In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every 3 to 6 months. As a minimum, this should include a disease-specific history, DRE and serum PSA determination, and is frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements. The testosterone level should be checked, especially during the first year.	C
Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression.	A
When disease progression occurs, or if the patient does not respond to the treatment given, the follow-up needs to be individualised.	C
In patients with suspected progression, the testosterone level must be checked. By definition, CRPC is based on the assumption that the patient is castrated (at least T < 50 ng/dL).	
Routine imaging of stable patients is not recommended.	B

18.8 References

1. Petros JA, Andriole GL. Serum PSA after antiandrogen therapy. Urol Clin North Am 1993 Nov;20(4):749-56. http://www.ncbi.nlm.nih.gov/pubmed/7505983
2. Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006 Aug;24(24):3984-90. http://www.ncbi.nlm.nih.gov/pubmed/16921051
3. Kwak C, Jeong SJ, Park MS, et al. Prognostic significance of the nadir prostate specific antigen level after hormone therapy for prostate cancer. J Urol 2002 Sep;168(3):995-1000. http://www.ncbi.nlm.nih.gov/pubmed/12187207
4. Collette L, de Reijke TM, Schröder FH; EORTC Genito-Urinary Group. Prostate specific antigen: a prognostic marker of survival in good prognosis metastatic prostate cancer? (EORTC 30892). Eur Urol 2003 Aug;44(2):182-9. http://www.ncbi.nlm.nih.gov/pubmed/12875936
5. Robinson D, Sandblom G, Johansson R, et al; Scandinavian Prostate Cancer Group (SPCG)-5. Prediction of survival of metastatic prostate cancer based on early serial measurements of prostate specific antigen and alkaline phosphatase. J Urol 2008 Jan;179(1):117-22; discussion 122-3. http://www.ncbi.nlm.nih.gov/pubmed/17997442
6. D'Amico AV, Moul JW, Carroll PR, et al. Intermediate end point for prostate cancer-specific mortality following salvage hormonal therapy for prostate-specific antigen failure. J Natl Cancer Inst 2004 Apr 7;96(7):509-15. http://www.ncbi.nlm.nih.gov/pubmed/15069112
7. Stewart AJ, Scher HI, Chen MH, et al. Prostate-specific antigen nadir and cancer-specific mortality following hormonal therapy for prostate-specific antigen failure. J Clin Oncol 2005 Sep 20;23(27):6556-60. http://www.ncbi.nlm.nih.gov/pubmed/16170163

8. Collette L, BurzyKowski T, Carroll KJ, et al. Is prostate antigen a valid surrogate end point for survival in hormonally treated patients with metastatic prostate cancer? Joint research of the European Organisation for Research and Treatment of Cancer, the Limburgs Universitair Centrum, and AstraZeneca Pharmaceuticals. J Clin Oncol 2005 Sep 1;23(25):6139-48. http://www.ncbi.nlm.nih.gov/pubmed/16135480
9. Strum SB, McDermed JE, Scholz MC, et al. Anaemia associated with androgen deprivation in patients with prostate cancer receiving combined hormone blockade. Br J Urol 1997 Jun;79(6):933-41. http://www.ncbi.nlm.nih.gov/pubmed/9202563
10. Daniell HW. Osteoporosis due to androgen deprivation therapy in men with prostate cancer. Urology 2001 Aug;58(2 Suppl 1):101-7. http://www.ncbi.nlm.nih.gov/pubmed/11502461
11. Miller PD, Eardley I, Kirby RS. Prostate specific antigen and bone scan correlation in the staging and monitoring of patients with prostatic cancer. Br J Urol 1992 Sep;70(3):295-8. http://www.ncbi.nlm.nih.gov/pubmed/1384920
12. Sissons GR, Clements R, Peeling WB, et al. Can serum prostate-specific antigen replace bone scintigraphy in the follow-up of metastatic prostatic cancer? Br J Radiol 1992;65(778):861-4. http://www.ncbi.nlm.nih.gov/pubmed/1384917
13. Scher HI, Halabi S, Tannock I, et al; Prostate Cancer Clinical Trials Working Group. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008 Mar 1;26(7):1148-59. http://www.ncbi.nlm.nih.gov/pubmed/18309951
14. Higano CS. Bone loss and the evolving role of bisphosphonate therapy in prostate cancer. Urol Oncol 2003 Sep-Oct;21(5):392-8. http://www.ncbi.nlm.nih.gov/pubmed/14670551
15. Tombal B, Berges R. Corrigendum to: How good do current LHRH agonists control testosterone? Can this be improved with Eligard®? [Eur Urol Suppl 4/8 (2005) 30-6]. Eur Urol 2006;49(5):937.
16. Morote J, Esquena S, Abascal JM, et al. Failure to maintain a suppressed level of serum testosterone during long-acting depot luteinizing hormone-releasing hormone agonist therapy in patients with advanced prostate cancer. Urol Int 2006;77(2):135-8. http://www.ncbi.nlm.nih.gov/pubmed/16888418
17. Yri OE, Bjoro T, Fossa SD. Failure to achieve castration levels in patients using leuprolide acetate in locally advanced prostate cancer. Eur Urol 2006 Jan;49(1):54-8; discussion 58. http://www.ncbi.nlm.nih.gov/pubmed/16314038
18. Sharifi R, Browneller R; Leuprolide Study Group. Serum testosterone suppression and potential for agonistic stimulation during chronic treatment with monthly and 3-month depot formulations of leuprolide acetate for advanced prostate cancer. J Urol 2002 Sep;168(3):1001-4. http://www.ncbi.nlm.nih.gov/pubmed/12187208
19. Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. J Urol 2009 May;181(5):1998-2006; discussion 2007-8. http://www.ncbi.nlm.nih.gov/pubmed/19286225
20. Braga-Basaria M, Dobs AS, Muller DC, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol 2006 Aug 20;24(24):3979-83. http://www.ncbi.nlm.nih.gov/pubmed/16921050
21. Tsai HK, D'Amico AV, Sadetsky N, et al. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst 2007 Oct 17;99:1516-24. http://www.ncbi.nlm.nih.gov/pubmed/17925537
22. Lu-Yao G, Stukel TA, Yao SL. Changing patterns in competing causes of death in men with prostate cancer: a population based study. J Urol 2004 Jun;171(6 Pt 1):2285-90. http://www.ncbi.nlm.nih.gov/pubmed/15126804
23. Shahani S, Braga-Basaria M, Basaria S. Androgen deprivation therapy in prostate cancer and metabolic risk for atherosclerosis. J Clin Endocrinol Metab 2008 Jun;93(6):2042-9. http://www.ncbi.nlm.nih.gov/pubmed/18349064
24. Mohile SG, Mustian K, Bylow K, et al. Management of complications of androgen deprivation therapy in the older man. Crit Rev Oncol Hematol 2009 Jun;70(3):235-55. http://www.ncbi.nlm.nih.gov/pubmed/18952456
25. Schwandt A, Garcia JA. Complications of androgen deprivation therapy in prostate cancer. Curr Opin Urol 2009 May;19(3):322-6. http://www.ncbi.nlm.nih.gov/pubmed/19318949

26. Conde FA, Aronson WJ. Risk factors for male osteoporosis. Urol Oncol 2003 Sep-Oct;21(5):380-3. http://www.ncbi.nlm.nih.gov/pubmed/14670549
27. Higano CS. Bone loss and the evolving role of bisphosphonate therapy in prostate cancer. Urol Oncol 2003 Sep-Oct;21(5):392-8. http://www.ncbi.nlm.nih.gov/pubmed/14670551
28. Hamdy RC, Baim S, Broy SB, et al. Algorithm for the management of osteoporosis. South Med J 2010 Oct;103(10):1009-15; quiz 1016. http://www.ncbi.nlm.nih.gov/pubmed/20818296

19. TREATMENT OF BIOCHEMICAL FAILURE AFTER TREATMENT WITH CURATIVE INTENT

19.1 Background

Primary curative procedures such as RP and RT are well-established therapeutic options in the management of localised PCa. Technical advances in surgery and RT have both improved the efficacy of treatment and reduced treatment-associated morbidity and toxicity.

Despite these improvements, however, there is still a significant risk of cancer recurrence after therapy. Between 27% and 53% of all patients undergoing RP or RT develop local or distant recurrences, and second-line treatment is required in 16-35% of cases within 10 and 5 years of the initial therapy, respectively (1-6).

19.2 Definitions

*19.2.1 **Definition of treatment failure***

Treatment failure was in the past defined as a recurrence identified during DRE or the development of metastatic disease. Currently, treatment failure is anticipated by a rising PSA level; Pound et al. (7) showed that no patients who were followed up for > 5 years developed a recurrence without a concomitant rise in PSA.

The PSA level that defines treatment failure differs between men who have undergone RP and those who have received RT. Following RRP, there is an international consensus that recurrent cancer may be defined by two consecutive PSA values of > 0.2 ng/mL (6,8). However, the most appropriate definition of biochemical progression after RP is still unclear. A retrospective analysis including 2,782 men who had undergone RP for clinically localised PCa (9) was used to determine the best PSA cut-off point for defining biochemical recurrence (BCR). Once PSA recurrence was detected, there was a subsequent increase in PSA in 49%, 62%, and 72% of patients with PSA levels of 0.2, 0.3, and 0.4 ng/mL, respectively (9). These data indicate that only half of patients with a PSA of 0.2 ng/mL will show further progression, and they can therefore be managed initially by surveillance.

This finding has been confirmed with similar data reported by Stephenson et al. (10), who identified a PSA value of > 0.4 ng/mL, followed by another increase, as the best cut-off level for indicating the development of distant metastases. This level was estimated using definitions obtained from a retrospective review of patients who had developed distant metastases following RP.

After RT, three consecutive increases in PSA following a PSA nadir were considered to provide a reasonable definition of BCR, according to the American Society for Therapeutic Radiology and Oncology (ASTRO) (11). This definition of PSA failure after RT was updated at the RTOG-ASTRO Phoenix Consensus Conference to any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir (12).

A recent study by Kapadia et al. including 710 patients with PCa who were treated with RT with or without ADT showed biochemical failure (BCF) in 21% at a median follow-up of 42 months after EBRT. Biochemical failure was present in 8%, 15%, and 36% of low-risk, intermediate-risk, and high-risk patients, respectively. The authors also found that there was a stronger correlation between a short interval to BCF (defined as failure occurring within 18 months of completing EBRT and/or ADT) and a significantly increased rate of distant metastases, decreased CSS, and decreased OS (13).

*19.2.2 **Definition of recurrence***

A recurrence of PCa can be defined as:

- Following RP, PSA values > 0.2 ng/mL, confirmed by two consecutive measurements
- Following RT, a PSA value of 2 ng/mL above the nadir after treatment

19.3 Local or systemic relapse

Once a PSA relapse has been diagnosed, it is extremely important to determine whether the recurrence has developed at local or distant sites. About 50% of patients who have undergone RRP will have local disease, while the remainder will have either distant disease alone or distant and local disease (11).

Several important parameters have been suggested in order to differentiate between local and distant relapse:
- Timing of the PSA increase after surgery.
- PSA velocity (PSAV).
- PSA doubling time (PSADT).
- Histopathological stage.
- Gleason score in the prostatectomy specimen.

Prostate-specific antigen increases developing within the first 2 years following surgery are more often associated with distant recurrences (12). It has been shown that a median PSADT of 4.3 months may be associated with distant relapse, whereas a median PSADT of 11.7 months is better predictive of local failure (14). Freedland et al. showed that clinical parameters, PSADT, pathological Gleason score, and time from surgery to BCR are important for stratifying patients into groups with varying levels of risk for prostate cancer-specific mortality (15). In patients who have undergone RP, there is apparently no indication for performing ultrasound-guided biopsies of the vesicourethral anastomosis in order to diagnose local relapse, as this method has low sensitivity and low predictive accuracy in patients with rising PSA levels < 1.0 ng/mL.

In patients who have undergone RT, any continuously rising PSA levels following a nadir after treatment indicate local recurrence, systemic metastatic spread, or a combination of the two (11,15,16). A late and slowly rising PSA level may be a sign of only local failure.

*19.3.1 **Ultrasensitive PSA***

The introduction of ultrasensitive PSA testing has made it possible to screen patients after RP and predict the risk of BCF after surgery at an early stage. Ultrasensitive PSA testing allows more precise measurement of the PSA nadir after radical surgery: patients with a PSA nadir < 0.01 ng/mL developed an early relapse in 4% of cases; by contrast, those with a PSA nadir of 0.04 ng/mL or higher developed an early relapse in 89% of cases (17).

*19.3.2 **Definition of local and systemic failure***

The definitions of local and systemic failure are as follows:
- Following RP, local failure is predicted with an 80% probability by a PSA increase 3 years after surgery, a PSADT > 11 months, a Gleason score < 7, and stage < pT3a pN0, pTx R1.
- Following RP, systemic failure is predicted with > 80% accuracy by a PSA increase at < 1 year after surgery, a PSADT of 4-6 months, a Gleason score of 8-10, and stage ≥ pT3b, pTx pN1.
- After RT, local failure is documented by a positive prostatic biopsy and negative imaging studies such as CT or MRI and bone scintigraphy. Prostatic biopsy after RT is considered necessary only if local procedures with curative intent, such as a salvage radical prostatectomy (SRP), are indicated in an individual patient.

19.4 Evaluation of PSA progression

Before extensive diagnostic work-up is carried out in patients with a PSA relapse following local treatment, men need to be stratified into those who are candidates for salvage therapy and those who are not. Any diagnostic procedures should only be performed if the results will have therapeutic consequences.

In recent years, most patients with PSA progression following initial therapy with curative intent have undergone physical and ultrasound examinations, as well as radiologic investigations or biopsies of the prostatic fossa and the vesicourethral anastomosis to confirm the recurrence suggested by serological studies. The diagnostic yield is very low in patients with asymptomatic PSA-only progression.

As mentioned above, according to Pound et al. (7), not all patients with BCF after RP also develop clinical recurrence. The authors evaluated the follow-up data for 1997 patients after RP, and only 34% of those with BCF subsequently had a clinical recurrence. These data have been confirmed by Boorjian et al. in a study including approximately 2400 patients; only a minority of those with BCF after RP developed a clinically evident recurrence (22.9%) and only few of them died due to PCa (5.8%) (18).

Imaging studies are used to distinguish between local relapse and systemic relapse in order to select the most appropriate treatment modality. Unfortunately, most imaging studies are not sensitive enough to identify the anatomic location of relapsing PCa at PSA levels < 0.5-1.0 ng/mL.

19.4.1 ***Diagnostic procedures for PSA relapse following RP***

Traditionally, bone scans and abdominal CT have been used to evaluate increases in the PSA level following primary treatment. Both imaging studies have low sensitivity and specificity, and can be safely omitted from the routine work-up for relapsing patients. Bone scans were examined in 144 patients presenting with PSA recurrences (20): 122 of the patients had undergone RP with no HT, and 22 had received either neoadjuvant or adjuvant ADT. In the first group, the lowest PSA associated with positive scintigraphy findings was 46 ng/mL, while in those who had received HT, the lowest PSA value was 15.47 ng/mL.

The probability of finding a positive bone scan remains < 5% until the serum PSA level reaches at least a value of 40 ng/mL. In other studies, patients with a true positive bone scan had an average PSA level of > 60 ng/mL and a PSAV of 22 ng/mL/year (21,22). Logistic regression analysis showed that PSA and PSAV were good predictors of bone scan results and that PSAV was a good predictor of CT scan results. Johnstone et al. (22) found a slight difference between surgically treated patients and those who received RT: 5% and 30% of the bone scans, respectively, were positive.

In summary, bone scintigraphy and abdominal CT scan are of no additional diagnostic value unless PSA serum levels are > 20 ng/mL or PSAV is > 20 ng/mL/year.

The diagnostic accuracy of endorectal MRI (e-MRI) using a 1.5-Tesla machine was investigated in a series of patients with PSA relapse following RP (23). The mean total PSA was 1.23 ± 1.3 ng/mL. The data were compared with standard references for local recurrence, including prostatectomy bed biopsy results, choline PET results, PSA reduction or increase after pelvic RT, and PSA modification during active surveillance. The sensitivity, specificity, positive and negative predictive values, and accuracy were 61.4%, 82.1%, 84.4%, 57.5%, and 69.4%, respectively, for unenhanced e-MRI and 84.1%, 89.3%, 92.5%, 78.1%, and 86.1%, respectively, for enhanced e-MRI. The two methods showed a statistically significant difference in accuracy (chi-squared test = 5.33, P = 0.02) and sensitivity (chi-squared test = 9.00, P = 0.0027).

Although e-MRI appears to be sensitive and predictive in identifying local recurrences following RP, it does not currently appear capable of becoming a routine imaging modality to be performed in every case, as local vs. systemic relapse may be differentiated at PSA levels < 0.5 ng/mL. At this level of PSA, e-MRI is not sufficiently sensitive or accurate.

Positron-emission tomography has been successfully used in many human cancers for early identification of local or systemic recurrences. In PCa, there are few, even if promising, published data on the clinical efficacy of PET in detecting local recurrences after RP, especially when an increased PSA value is detected (24-28). Choline, as a component of the phosphatidylcholines, is highly increased in PCa and can be easily radiolabeled with either carbon-11 (^{11}C-choline) or fluorine-18 (^{18}fluorocholine).

Kotzerke et al. (24) reported a potential use of ^{11}C-acetate PET as a new tool for diagnosing PCa recurrences, with an important impact on management as well. However, Cimitan et al. (25) suggested that in previously treated PCa patients with biochemical recurrences, ^{18}F-choline PET/CT may not have a significant impact on therapeutic care until PSA increases to > 4 ng/mL, particularly in patients with well or moderately differentiated primary tumors (Gleason score ≤ 7). Choline PET/CT may be helpful in selected patients with higher PSA levels and/or poorly differentiated PCa (Gleason score > 7), to exclude distant metastases when salvage local treatment is intended.

Pelosi et al. (29) reported that the sensitivity of ^{18}F-choline PET/CT was 20%, 44%, and 80% in patients with PSA levels ≤ 1 ng/mL, 1-5 ng/mL, and > 5 ng/mL, respectively. Husarik et al. (30) evaluated the accuracy of PET/CT for detecting relapses following initial radical treatment for PCa. They confirmed that it is more accurate in patients with PSA levels > 2 ng/mL, regardless of the concomitant use of HT.

Giovacchini et al. (27) reported that PSAV was a predictor of positive ^{11}C-choline PET/CT and that it can be used to stratify the risk of positive ^{11}C-choline PET/CT in PCa patients with BCF. The authors concluded that a PSAV rate of > 1 ng/mL/year should be used to increase the rate of positive detection with ^{11}C-choline PET/CT. The most recent series evaluating the role of ^{11}C-choline PET/CT in men with biochemical failure after RP showed that metastases were more likely to be identified at higher PSA levels, with a detection rate ranging

from 20% to 36% in patients with PSA levels < 1 ng/mL and increasing to 63-83% in men with PSA levels > 3 ng/mL (31-33).

Recently, Giovacchini et al. (34), evaluating 109 patients with rising PSA levels and negative conventional imaging studies, concluded that ^{11}C-choline PET/CT may be helpful for re-staging PCa, but it should not be used to guide therapy. The use of ^{11}C-choline PET/CT in all men with a rising PSA level > 1 ng/mL would result in an 85% incidence of unnecessary examinations, a significant increase in medical costs, and no benefit for the individual patient.

Graute *et al*. (35) used ^{18}F PET/CT to try to identify PSA threshold levels, as well as the PSAV, progression rate, and PSADT in relation to the detectability and localisation of recurrent lesions. ROC analysis identified the optimal threshold for distinguishing between PET-positive and PET-negative findings as 1.74 ng/mL (AUC 0.818), resulting in a sensitivity of 82% and a specificity of 74%. In that study, the sensitivity for tumor detection correlated with serum PSA levels, yielding sensitivities increasing from 20% in patients with PSA ≤ 1 to 44% for PSA ≤ 5 ng/mL and 82% for PSA > 5 ng/mL.

Fuccio et al. (26) evaluated consecutive patients with biochemical recurrences (mean PSA value 3.3 ng/mL) after RP. Using ^{11}C-choline PET/CT, they identified unknown bone lesions in 14.6% of the patients; 33% of these lesions did not reveal any structural change at CT. As previously reported in the literature, the advantage of choline PET/CT may be that it is able to detect bone marrow involvement in PCa patients at an early stage before and after therapy (36,37).

The effects of HT on radiolabeled choline uptake (especially in the skeleton) are of great importance and still under investigation. Giovacchini et al.(38) evaluated the influence of HT on the efficacy of choline PET. Although HT was significantly associated with an increased risk of positive choline PET/CT in the univariate analysis, the effects of ADT were no longer significant in the multivariate analysis.

As recently reported by Picchio *et al*. (39), routine use of ^{11}C-choline PET/CT cannot be recommended for PSA values < 1 ng/mL, but a cut-off value for appropriate referral of patients for choline PET/CT imaging has yet to be defined. The accuracy of PET correlates with PSA values, PSADT, and other pathological features. Certainly, a PSADT < 3 months can be regarded as a strong predictor of PET positivity.

Panebianco et al. compared the accuracy of detecting local recurrence of PCa in patients with BCF using proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) in comparison with combined dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) techniques with a 3 T magnet vs. ^{18}F-choline PET/CT. ^{1}H-MRS-DCEMR combined techniques may be a valid tool for detecting PCa recurrence and may be more accurate than PET/CT for identifying smaller lesions in patients with low biochemical alterations after RRP (0.2-2 ng/mL) (sensitivity 92% vs. 62%; specificity 75% vs. 50%; accuracy 89% vs. 60%) (40).

In summary, the role and diagnostic accuracy of ^{11}C-choline PET/CT in men with rising PSA following RP depends on the absolute PSA value, PSADT, and PSAV. The higher the PSA level and the faster the PSADT, the better will be the predictive value of this imaging modality. However, even in patients with PSA values > 2 ng/mL and negative imaging studies, ^{11}C-choline PET/CT is positive in only 28% of patients. It appears that there is an urgent need for well-conducted and histologically controlled trials to explore the potential role of ^{11}C-choline PET/CT.

19.4.2 ***Diagnostic studies for PSA relapse following radiation therapy***

With regard to PSA relapses following RT, routine prostate biopsy should no longer be performed for the evaluation of PSA-only recurrences, according to an ASTRO consensus recommendation (11). However, a prostate biopsy documenting local recurrence represents the main cornerstone in the decision-making process for SRP in patients with rising PSA levels following a nadir after RT (41). It is a general recommendation to wait about 18 months and 3 months after RT or seed implant and cryotherapy or high-intensity focused ultrasound (HIFU), respectively. Patients with rising PSA and a viable cancer on biopsy 2 years after RT have true locally recurrent disease and may be candidates for SRP.

The role of choline PET/CT to detect local or systemic recurrences in men with a PSA relapse following RT is still unclear and based on very few studies (42,43). No conclusive recommendations can therefore be made. The sensitivity and specificity of choline PET/CIT with regard to the detection of lymph node metastases are less reliable, and routine use of ^{11}C-PET cannot therefore be recommended, especially for PSA values < 1 ng/mL.

The role of e-MRI, MRI spectroscopy, and dynamic contrast-enhanced MRI for the identification of locally recurrent PCa following RT was evaluated in a number of studies (44-46). These studies have demonstrated that locally recurrent PCa can be differentiated from benign nodules due to its low signal intensity on T2-weighted imaging. e-MRI and magnetic resonance spectroscopy were more sensitive than transrectal ultrasonography (TRUS) or TRUS-guided prostate biopsies for detecting viable PCa. e-MRI also contributed important information regarding the presence of extraprostatic extension and seminal vesicle invasion, with a sensitivity of 86% and a specificity of 96%. e-MRI is therefore strongly recommended in the diagnostic work-up of men with a PSA relapse after RT, who may be candidates for secondary local salvage therapy with curative intent.

19.5 Treatment of PSA-only recurrences

The timing and mode of treatment for PSA-only recurrences after RP or RT are still controversial. After RP, the therapeutic options are:

- Radiotherapy to the prostatic bed.
- (Complete) androgen deprivation (CAD, AD).
- Intermittent androgen deprivation (IAD).
- Combination of antiandrogens with 5-alfa-reductase inhibitors.
- Early chemohormonal approaches.

Following RT, the same therapeutic options may apply in relation to PSA recurrences. In addition, SRP, cryotherapy, or brachytherapy may be indicated in carefully selected patients.

*19.5.1 **Radiotherapy for PSA-only recurrence after RP***

Three large randomised controlled trials in adjuvant radiation have been published (47-49). All three reported a BCR-free survival benefit with adjuvant RT of at least 15% at 5 and 10 years.

The largest trial (EORTC-22911, n = 1005) (47) and the smallest trial (ARO-96-02, n = 307) (49) trial were powered to detect a benefit in BCR-free survival, while metastasis-free survival was the primary end-point of the third trial (SWOG-S8794, n = 431) (48). The three trials had similar inclusion criteria. However, the EORTC trial also included pT2 R1 patients, while the other two trials allowed only pT3 cancers with or without positive resection margins. Quite a high proportion of patients in all three trials (63-68%) had positive surgical margins.

It should be noted that the postoperative PSA level before patients were randomly assigned to adjuvant RT differed among the three trials. In the German ARO-96-02 trial, only men with a PSA < 0.1 ng/mL were eligible for randomisation; in the EORTC trial, 11% of men had a PSA level > 0.2 ng/mL prior to randomisation, and 34% in the SWOG trial. Thus, a substantial number of men in the EORTC and SWOG trials received “salvage” radiotherapy (SRT) rather than “adjuvant” RT for a non-normalised PSA. It is therefore of interest that not all of the men in the nonadjuvant arms of the trials were treated with SRT by the time of a biochemical recurrence: delayed RT or SRT to the prostatic fossa was administered in 55% of men with a rising PSA level in the EORTC trial and to 33% of men in the SWOG trial. Thus, the trials were not able to evaluate whether adjuvant radiation was superior to salvage radiation as in the control arm; only half of the men received RT at the time of PSA recurrence.

The authors of the EORTC trial suggested that SRT may be equivalent to adjuvant therapy, provided that the PSA level is < 1 ng/mL (47). However, only the SWOG trial was powered to address the effect of delayed radiation, as it was the only trial with metastasis-free survival as the primary end-point. In the SWOG trial, men in the control arm were less likely to receive SRT (33%). However, it took a median follow-up of over 12 years before metastasis-free survival improved in the adjuvant treatment arm, suggesting that adjuvant therapy may not be helpful in men with a life expectancy of less than 10 years (48,49). Recently, it has been demonstrated that patients in the control group more often had a higher frequency of PCa with Gleason score 8-10 and were more likely not to receive ADT at the time of PSA relapse.

There have been many studies on the use of RT for PSA-only recurrences after RRP. As a result, there is a growing body of parameters for predicting the outcome that may help differentiate between the need for observation, RT, or HT. As confirmed by various studies, the pre-radiotherapy PSA level is critically important for optimal treatment results (41,44,45).

Cotter et al. analysed 4,036 patients with 11.3 years of follow-up who had been treated with RP for PCa, and found that SRT was associated with a significant reduction in all-cause mortality for men with either a PSADT of < 6 months or a PSADT of ≥ 6 months (50).

Siegmann et al. tried to define "what is the best time to treat" patients with biochemical recurrences after RP. They evaluated the biochemical response to SRT, without HT, in 301 patients, with a median follow-up of 30 months. In the multivariate logistic regression analysis evaluating factors influencing an undetectable PSA following SRT, only the pre-SRT PSA level (odds ratio 2.62, P = 0.001) and infiltration of the seminal vesicles (odds ratio 2.53, P = 0.02) were found to be independent predictive factors. The authors found that patients with a PSA level < 0.28 ng/mL before SRT had a better outcome than those with higher PSA levels and that they may have a chance of a long-term durable response without further treatment (51). Similarly, a major role for early SRT was reconfirmed by a systematic review by Ohri et al., who demonstrated that the biochemical recurrence-free survival (BCR-FS) increased along with the SRT dosage by 2.5% per Gy and decreased along with the pre-SRT PSA by 18.3% per ng/mL (P < 0.001) (52).
ASTRO has published a consensus paper recommending a dosage of at least 64 Gy when the PSA level is < 1.5 ng/mL after RRP (11).

Stephenson et al. evaluated prognostic models for predicting the outcome of SRT in a cohort of 1603 men with PSA progression after RP who underwent surgery in 17 North American tertiary referral centres. They identified a significant relationship between the PSA value at the time of RT and the therapeutic outcomes. Specifically, the 6-year BCR-FS estimates were 48% in men with PSA < 0.5 ng/mL and only 40%, 28%, and 18% in men with PSA levels of 0.51-1.0 ng/mL, 1.01-1.50 ng/mL, and > 1.50 ng/mL, respectively (53).

In the SWOG and EORTC nonadjuvant radiotherapy arms, the median intervals to SRT were 2.0 and 2.2 years, respectively. In the SWOG 8974 study, 23% of men had a PSA level > 1.5 ng/mL prior to SRT. In a subanalysis of the SWOG 8,974 trial, Swanson et al. (54) showed that men in all categories of post-prostatectomy PSA levels (< 0.2, 0.2-1.0, > 1.0 ng/mL) had improved metastasis-free survival after SRT. However, the therapeutic benefit was most evident in the presence of minimal PSA serum levels. These data suggest that, although less effective, SRT may help improve the metastasis-free survival.

In a multi-institutional, matched-control analysis of adjuvant and salvage postoperative RT for pT3-4 N0 PCa, Trabulsi et al. (55) demonstrated a BCR-FS advantage in favor of adjuvant RT vs. SRT. Interestingly, in a multivariable Cox regression analysis, adjuvant RT vs. SRT was not an independent predictor of metastatic PFS, after correction for adverse clinical and pathological factors.

Data have become available on overall survival and SRT. In a group of men with a median follow-up of 9 years after radical prostatectomy, the benefit of SRT for PCa-specific mortality was seen particularly in men with a PSADT of less than 6 months who had received SRT to the prostate fossa within 2 years after a rise in PSA (56). This suggests that local disease control may prolong the prostatic CSS in men formerly thought to be at risk for systemic disease progression and less likely to benefit from (salvage) RT.

Men with slowly progressing disease, although they are still at risk for systemic progression, may not benefit from SRT as they have a low risk for developing fatal PCa. Longer follow-up periods are certainly needed in order to answer this question.

19.5.1.1 Dose, target volume, toxicity
The three randomised trials on adjuvant RT all used dosages < 66 Gy, which is currently the most frequently used dosage for adjuvant and salvage RT. However, it is important to note that, as with dose escalation studies in primary radiation for PCa, an increased dose in the salvage setting may improve the biochemical response without worsening local toxicity (57,58). Dosages of up to 70 Gy have shown better BCR-free rates at higher dosages, with 66.8 Gy RT found to be the dosage required for 50% BCR-free survival. Even higher doses may be considered, particularly when using improved imaging techniques, such as fiducial markers (59). The finding that 9% of men develop a local recurrence after adjuvant radiation of 60 Gy provides support for an increase in the dosage and target volume (54).

Target volume delineation has been found to vary by up to 65% between different radiotherapists administering adjuvant or salvage radiation to the prostatic fossa (60-62). It is therefore important not to overlook local toxicity. In the EORTC 22911 study, 3.1% of men had to interrupt adjuvant RT because of local symptoms, mainly diarrhoea. Although grade 3 or 4 toxicity is rare for either adjuvant or SRT to the prostate fossa, it was almost doubled in the adjuvant arm of the EORTC 22911 study (2.6% vs 4.2%) and the SWOG S8794 study, particularly with regard to urethral strictures (relative risk 9) and incontinence (relative risk 2.3).

19.5.2 ***Hormonal therapy***
Systemic failure following RP is predicted with > 80% accuracy by a PSA relapse < 1 year, a PSADT of 4-6 months, Gleason score 8-10, and stage pT3b, pTx pN1. There is some evidence that early HT may help delay progression and possibly achieve a survival benefit (63,64).

19.5.2.1 Adjuvant hormonal therapy after RP

In the absence of randomised controlled trials for postoperative PSA recurrence, it is necessary to rely on retrospective data or to extrapolate data from other clinical settings, such as men with metastatic disease or locally advanced nonmetastatic disease. It is uncertain whether or not such data are relevant to men with rising postoperative PSA levels.

Two randomised studies have compared immediate HT (after diagnosis) with deferred HT (on progression) in patients with PCa. The Medical Research Council study in locally advanced or asymptomatic metastatic PCa and the EORTC study in newly diagnosed PCa (T0-4 N0 M0) illustrate that, although immediate HT after diagnosis may delay disease progression in men with PCa, this does not necessarily result in an improved CSS (65,66).

A survival advantage for immediate (adjuvant) ADT after RP has only been confirmed in patients with positive lymph node PCa in a single randomised study (63,64).

Mydin et al. concluded that early salvage HT based on PSA ≤ 10 ng/mL and absent distant metastases improved the survival in patients with PCa after the failure of initial treatment with neoadjuvant HT plus RT (67).

Adjuvant bicalutamide (150 mg) was able to decrease progression in men with locally advanced PCa, but did not result in an OS benefit (68). Several retrospective analyses from the Mayo Clinic have shown that adjuvant HT after RP had a positive effect on the time to progression and cancer death in pT3b and N+ patients (69-71). However, large series from the Mayo Clinic with a median follow-up of 10.3 years show that adjuvant HT in surgically managed N+ patients decreased the risk of BCF and local recurrence, but did not have a significant impact on systemic progression or CSS (72). Another retrospective study with a median follow-up period of 5.2 years showed that immediate and delayed HT (at PSA recurrence) in surgically managed N+ patients provided similar outcomes (73).

An observational study has shown that deferred vs. immediate ADT in N+ men after RP may not significantly compromise survival. There was no statistically significant difference in the OS between the adjuvant ADT group and the non-ADT group. These results need to be validated in a prospective study (74).

19.5.2.2 Postoperative hormonal therapy for PSA-only recurrence

Androgen deprivation therapy

Although patients with postoperative PSA recurrences often undergo ADT before there is any evidence of metastatic disease, the benefit of this approach is uncertain. A retrospective study including 1,352 patients with postoperative PSA recurrence showed no significant difference in the time to clinical metastases with early ADT (after PSA recurrence, but before clinical metastases) vs. delayed ADT (at the time of clinical metastases). However, after risk stratification, it was found that early ADT was able to delay the time to clinical metastases in high-risk patients with a Gleason score > 7 and/or a PSADT < 12 months. ADT had no overall impact on the PCa-specific mortality (75).

It has been shown (76) that adjuvant ADT (within 90 days of surgery) slightly improved the CSS and systemic PFS after RP in a large group of high-risk PCa patients. The survival advantage was lost when ADT was administered later in the disease process, at the time of PSA recurrence or systemic progression. It should be emphasised that there was no advantage with regard to OS (83% in both groups) and that the differences in the CSS and systemic PFS were only 3% and 5%, respectively. In a retrospective study including 422 patients with postoperative PSA recurrences, 123 developed distant metastasis, of whom 91 patients with complete data received deferred ADT at the time of documented metastasis after RP. It was concluded that when closely followed up after PSA recurrence, patients may have an excellent response to deferred ADT and a long survival period, with a median failure time of 169 months from RP to death (77). These three studies are limited by their retrospective design and in assessing the side effects of long-term ADT. They do not allow any definitive conclusions to be drawn on the use of early HT in clinical practice.

Antiandrogens

Although gynecomastia and breast tenderness were the most predominant side effects of treatment for organ-confined and locally advanced PCa, the incidence of hot flushes, loss of libido, and impotence was significantly lower than expected for luteinising hormone-releasing hormone (LHRH) agonists and complete androgen deprivation (CAD) (78).

However, the OS did not differ between the groups (79). Low-dose flutamide (250 mg daily) is currently being investigated in men with PSA recurrences.

Intermittent androgen deprivation

Intermittent androgen deprivation (IAD) has been examined as a potential alternative to CAD in order to:

- Delay the time to androgen independence and hormone-refractory disease.
- Minimise side effects.
- Reduce the costs of prolonged therapies.

There are no long-term data from large-scale randomised controlled trials that can confirm the superiority of IAD over CAD for survival. Limited information suggests that IAD may result in a slight reduction of adverse effects (80). However, in the setting of PSA-only recurrences, there are no prospective randomised trials and no clinical studies with sufficient data on long-term efficacy to justify the routine clinical application of IAD, despite its potential benefits.

In the series in which PSA-only recurrences were treated with IAD (81-84), PSA threshold levels at study entry varied significantly, as did the PSA level at discontinuation of HT. Crook et al. randomly assigned 690 patients to IAD and 696 to CAD. There were no significant between-group differences with regard to adverse events; in the IAD group, full testosterone recovery occurred in 35% of patients, and testosterone recovery to the trial-entry threshold occurred in 79%. Intermittent androgen deprivation provided potential benefits with respect to physical function, fatigue, urinary problems, hot flushes, libido, and erectile function (85).

Minimal androgen blockade

In some studies, finasteride and flutamide have been combined for the management of PSA-only recurrences, since the two agents work additively by blocking the intraprostatic conversion of testosterone to dihydrotestosterone (DHT) and blocking the intracytoplasmic DHT receptor (86-88). In the latest report (87), including 73 patients, administration of finasteride (10 mg/day) and low-dose flutamide (250 mg/day) resulted in a mean PSA nadir of 1.35 ng/mL within 6 months. However, only 62% of the patients studied reached a PSA nadir of < 0.2 ng/mL.

After a mean follow-up period of 15 months, none of the patients had progressed to traditional HT. However, longer follow-up of a larger patient cohort is needed, and randomised phase III trials using modern antiandrogens with fewer gastrointestinal and hepatic side effects are mandatory.

Hormonal therapy after RP combined with radiotherapy and/or chemotherapy

The addition of HT to SRT (n = 78) was not associated with any additional increase in the CSS (88). A phase II trial including 74 patients with postoperative PSA recurrences showed that combined treatment with SRT plus 2 years of CAD (castration + oral antiandrogen) had relatively minor long-term effects on quality of life (89). However, more efficacy data are needed and the potential increase in side effects should be considered when combining therapies. Results are eagerly awaited from a recently completed randomised controlled phase III study from the Radiation Therapy Oncology Group (RTOG-9061) comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the postoperative setting.

Radiotherapy and ADT in combination after local surgery are being investigated in a recently started, large, randomised, controlled study sponsored by the Medical Research Council. The study is addressing the timing of RT (adjuvant vs early salvage) and the duration of HT (none vs. short-term vs. long-term) used together with postoperative RT. The primary outcome measure will be CSS. Secondary outcome measures will include OS, ADT administered outside the protocol, and reported treatment toxicity. The study is also aiming to assess the long-term effect of RT after RP on sexual, urinary, and bowel function, and the long-term effect of ADT on sexual function and the overall quality of life (90).

Currently, it seems there is no indication for chemotherapy in patients with PSA-recurrence only. Chemotherapy should be considered as a treatment option for patients with castration-resistant PCa, but when a cytotoxic regimen should be initiated is still a matter of controversy (91).

*19.5.3 **Observation***

Observation until the development of clinically evident metastatic disease may represent a viable option for patients with a Gleason score < 7, PSA recurrence > 2 years after surgery, and a PSADT of > 10 months. In these patients, the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years (7).

*19.5.4 **Management of PSA relapse after radical prostatectomy***

Recommendations	GR
Local recurrences are best treated by salvage RT with 64-66 Gy at a PSA serum level < 0.5 ng/mL.	B
For patients with presumed local recurrence who are too unfit or who are unwilling to undergo RT, expectant management can be offered.	B
PSA recurrence indicative of systemic relapse is best treated by early ADT, resulting in a reduced frequency of clinical metastases.	B
LHRH analogues/antagonists/orchiectomy or bicalutamide (150 mg/day) can be used when there is an indication for HT.	A

ADT= androgen deprivation therapy; HT = hormone therapy; LHRH = luteinising hormone-releasing hormone; PSA = prostate-specific antigen; RT = radiotherapy.

19.6 Management of PSA failures after radiation therapy

In a review of data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), including 2336 patients with PCa, Grossfeld et al. (92) demonstrated that 92% of patients who had initially been treated with RT received ADT for secondary treatment of PSA progression, with no salvage procedures. The mean time interval from biochemical to clinical progression is approximately 3 years. Therapeutic options in these patients are ADT or local procedures such as salvage RP, cryotherapy, and interstitial RT (41,93-101). Salvage radiotherapy has not gained widespread acceptance because of the morbidity associated with it - namely, urinary incontinence (UI), local recurrences, and rectal injuries. However, in well-selected patients, the procedure may result in long-term disease-free survival.

*19.6.1 **Salvage radical prostatectomy***

Previously, most series reporting on SRP have included patients treated in the pre-PSA era without modern radiotherapeutic techniques, when local recurrences were usually detected at a late stage. Complications associated with the procedure were therefore quite high, with up to 65% of patients suffering from treatment-related morbidity. Up to 60% of patients who underwent SRP had to undergo anterior or total exenteration for locally extensive disease, associated with a high rate of local recurrences and a mean time to progression of 1.3 years.

Recent reports analysing patients who were operated on during the past decade have described much more optimistic outcomes after SRP. In a recent systematic review of the literature, Chade et al. showed that SRP allowed 5-year and 10-year biochemical recurrence-free survival (BCR-FS) estimates ranging from 47% to 82% and from 28% to 53%, respectively. The 10-year cancer-specific and OS rates ranged from 70% to 83% and from 54 to 89%, respectively. The pre-SRP PSA value and prostate biopsy Gleason score were the strongest predictors of the presence of organ-confined disease, progression, and CSS. The authors also highlighted that the associated surgical morbidities were acceptable in the hands of experienced surgeons (102).

In a multicentre series, at 10 years after SRP, Chade et al. reported a BCR-FS of 37%, a metastasis-free survival of 77%, and a CSS of 83%. In a preoperative multivariate analysis in the study, the pre-SRP PSA and the Gleason score at post-radiotherapy prostate biopsy were found to be predictive of biochemical recurrence (103).

In the series reported by Garzotto and Wajsman (97), 24 patients underwent radical cystoprostatectomy or RP with neoadjuvant ADT. Neoadjuvant ADT was associated with a lower rate of positive surgical margins (21%) in comparison with patients in whom ADT failed, who had a positive surgical margin rate of 80%. The authors showed that the disease-specific survival correlated strongly with surgical margin status. After a mean follow-up period of 5 years, the disease-specific survival rates were 95% and 44% for those with negative and positive surgical margins, respectively. Vaidya and Soloway reported a low rate of complications, good postoperative continence, and only one biochemical recurrence 36 months after SRP (98). Similar data have been described by Stephenson *et al*. (99).

In most contemporary series, organ-confined disease, negative SMs, and an absence of seminal vesicle and/or lymph node metastases were favorable prognostic indicators associated with a better disease-free survival of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa (100).

Heidenreich *et al*. (101) reported on the oncological and functional outcome in 55 patients who underwent radical salvage therapy for locally recurrent PCa after various types of modern state-of-the-art RT, performed in or after the year 2000. Forty (72.7%) and 15 (27.3%) patients demonstrated organ-confined and locally advanced PCa, respectively. Eleven patients (20%) and seven patients (14%) had lymph node metastases and

positive surgical margins, respectively. In the multivariate analysis, significant predictors of organ-confined PCa with negative surgical margins were:

- Biopsy Gleason score prior to SRP ($P = 0.02$)
- < 50% positive biopsy cores ($P = 0.001$)
- PSADT > 12 months ($P = 0.001$)
- Low-dose brachytherapy ($P = 0.001$)

Urinary continence was achieved after a mean of 8 months in virtually all men after low-dose brachytherapy, while UI persisted in about 20% of patients who underwent EBRT or high-dose brachytherapy.

More recently, salvage laparoscopic radical prostatectomy (SLRP) has been suggested by Ahallal et al. The authors analysed the data for 15 patients who underwent SLRP for biochemical recurrences after RT. Continence recovered in about 50% of the patients, and erectile dysfunction occurred in nearly all of them. The biochemical control was similar to that with the open technique (104).

The current status of salvage robotic RP is still under investigation (105).

19.6.1.1 Summary of salvage radical prostatectomy

In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, an organ-confined PCa < T2, Gleason score < 7, and preoperative PSA < 10 ng/mL. In all other patients, accurate preoperative staging is not easily defined after RT, increasing the risk not only for anterior and total extirpation procedures, but also for associated complications and reduced long-term disease-specific survival.

*19.6.2 **Salvage cryoablation of the prostate***

In cases in which RT fails, salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the 5-year biochemical disease-free survival estimates ranged from 50% to 70%. With the use of third-generation technology, severe complications such as rectourethral fistulae have been significantly less common over the last decade than in the past (106).

According to Cespedes et al. (107), the risks of UI and erectile dysfunction at least 12 months after SCAP were as high as 28% and 90%, respectively. In addition, 8-40% of patients reported persistent rectal pain, and an additional 4% of the patients underwent surgical procedures for the management of treatment-associated complications.

With regard to the oncological outcome, studies have shown that a durable PSA response can be achieved in about 50% of patients with a pre-SCAP PSA < 10 ng/mL (108).

In a multicentre study reporting the current outcome of SCAP in 279 patients, the 5-year BCR-free survival estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15 of the 46 patients (32.6%) who underwent prostate biopsy after SCAP. The UI rate was 4.4%. The rectal fistulae rate was 1.2%, and 3.2% of patients had to undergo transurethral resection of the prostate (TURP) for removal of sloughed tissue (109).

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCa after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 in the SRP group and 5.5 years in the SCAP group. The 5-year BCR-free survival was 61% following SRP, significantly better than the 21% detected after SCAP. The 5-year OS was also significantly higher in the SRP group (95% vs. 85%) (110).

*19.6.3 **Salvage brachytherapy for radiotherapy failure***

Experience with salvage brachytherapy for patients in whom RT has failed is very limited. In a small study including 11 patients treated with high-dose brachytherapy after RT failure, Jo et al. reported that seven of the 11 patients were free of recurrent disease after a mean of 29 months of follow-up (111). Beyer (112) reported that 34-53% of patients remained free of biochemical relapse after 5 years, with local cancer control achieved in 98% of the patients. However, the complication rate was quite high:

- 27% of the patients became incontinent.
- 14% needed palliative TURP due to acute urinary retention.

- 4% developed rectal ulcers.
- 2% required a permanent colostomy.

A recent review of salvage brachytherapy for RT failure by Gomez-Veiga et al. reported 5-year BCR-free survival rates ranging from 20% to 87%. A single study reported a 10-yearr BCR-free survival rate of 54% (113).

Moman et al. (114) retrospectively evaluated the outcome and toxicity after salvage iodine-125 implantation in 31 patients with locally recurrent PCa after primary iodine-125 implantation and EBRT. The mean follow-up period was 9 years (SD ± 4). The rates of freedom from BCR were 51% and 20% after 1 and 5 years of follow-up, respectively. Grade 1, 2, or 3 toxicity of the genitourinary tract was reported in 29%, 58%, and 3% of the patients, respectively, in the acute phase, and in 16%, 39%, and 19%, respectively, in the late phase. Grade 1, 2, or 3 toxicity of the gastrointestinal tract was reported in 45%, 10%, and 0% of the patients, respectively, in the acute phase, and in 48%, 3%, and 6%, respectively, in the late phase.

In conclusion, freedom from BCR after salvage iodine-125 implantation for locally recurrent PCa following RT is limited, and both genitourinary and gastrointestinal toxicity occur frequently.

19.6.4 ***Observation***

Patients who have signs of only local recurrence (i.e., low-risk patients with late recurrence and a slow PSA rise) who do not wish to undergo second-line curative options are best managed by observation alone. A retrospective cohort analysis of HT vs. watchful waiting in 248 men with PSA failure after RT showed no advantage for HT in the subgroup of men with a PSADT of > 12 months after RT. The 5-year metastasis-free survival rate was 88% with hormone therapy versus 92% with watchful waiting ($P = 0.74$) (115).

19.6.5 ***High-intensity focused ultrasound***

Experience with high-intensity focused ultrasound (HIFU) for the treatment of locally recurrent PCa after RT is limited to a few retrospective studies. Zacharakis et al. (116) investigated the oncological and functional outcome of HIFU in a cohort of 31 men with biopsy-proven locally recurrent PCa following EBRT. The mean preoperative PSA level was 7.73 ng/mL (range 0.20-20.0 ng/mL). The patients were followed up for a mean of 7.4 months (range 3-24 months). Side effects included stricture or intervention for necrotic tissue in 11 patients (35%), urinary tract infection or dysuria syndrome in eight (26%), and UI in two (6%). Rectourethral fistulae occurred in two men (7%). Overall, 71% had no evidence of disease following salvage HIFU.

Murat et al. (117) evaluated the safety and efficacy of salvage HIFU in 167 patients with local PCA recurrence after EBRT and assessed prognostic factors for optimal patient selection. Local cancer control was achieved with negative biopsy results in 122 patients (73%). The median PSA nadir was 0.19 ng/mL. The mean follow-up period was 18.1 months (range 3-121 months). Seventy-four patients did not require HT. The actuarial 5-year OS rate was 84%. The actuarial 3-year progression-free survival was significantly lower in case of:

- High pre-EBRT stage (with estimates as low as 53%, 42%, and 25% for low-risk, intermediate-risk, and high-risk patients, respectively).
- High pre-HIFU PSA.
- Use of ADT during PCa management.

Specifically, patients in the intermediate-risk and high-risk groups had a 1.32-fold and 1.96-fold higher risk, respectively, of any-cause mortality in comparison with the low-risk group. Moreover, patients treated with ADT had also a 2.8-fold higher risk of death in comparison with those who did not undergo ADT. No rectal complications were observed. Urinary incontinence accounted for 49.5% of the urinary sphincter implantations required in 11% of patients.

Urinary incontinence and the development of rectourethral fistulae are the most significant complications of salvage HIFU therapy (116-118). About 30% of men develop some form of incontinence, with significant UI treated with an artificial urinary sphincter in about 10% of patients. The oncological control rate after a short median follow-up period of about 2 years is 30-40%.

19.6.6 *Guidelines for the management of PSA relapse after radiotherapy*

Recommendations	GR
Local recurrences can be treated with salvage RP in carefully selected patients, who presumably have organ-confined disease - i.e., PSA < 10 ng/mL, PSADT > 12 months, low-dose brachytherapy, biopsy Gleason score < 7.	B
Cryosurgical ablation of the prostate and interstitial brachytherapy are alternative procedures in patients not suitable for surgery	B
HIFU may be an alternative option. However, patients must be informed about the experimental nature of this treatment modality, due to the short follow-up periods reported.	
In patients with presumed systemic relapse, ADT may be offered.	B

ADT = androgen deprivation therapy; HIFU = high-intensity focused ultrasound; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; RP = radical prostatectomy.

19.7 Guidelines for second-line therapy after treatment with curative intent

Recommendations	GR
Presumed local failure after radical prostatectomy:	
Patients with presumed local failure only may be candidates for salvage RT. This should be given with at least 64 Gy and preferably before PSA has risen above 0.5 ng/mL.	B
Other patients are best offered a period of watchful waiting (active monitoring), with possible HT later on.	
Presumed local failure after radiotherapy:	
Selected patients may be candidates for SRP, and patients should be informed about the higher risk of complications - e.g., urinary incontinence and erectile dysfunction.	C
SRP should only be performed in experienced centres.	
Other patients are best offered a period of watchful waiting (active monitoring), with possible HT later on.	
Presumed distant failure:	
There is some evidence that early HT may be of benefit with or without local failure, delaying progression and possibly achieving a survival benefit in comparison with delayed therapy. The results are not uncontroversial.	B
Local therapy is not recommended except for palliative reasons.	

HT = hormone therapy; PSA = prostate-specific antigen; RT = radiotherapy; SRP = salvage radical prostatectomy.

19.8 References

1. Grossfeld GD, Stier DM, Flanders SC, et al. Use of second treatment following definitive local therapy for prostate cancer: data from the CaPSURE database. J Urol 1998;160(4):1398-404. http://www.ncbi.nlm.nih.gov/pubmed/9751363
2. Lu-Yao GL, Potosky AL, Albertsen PC, et al. Follow-up prostate cancer treatments after radical prostatectomy: a population-based study. J Natl Cancer Inst 1996;88(3-4):166-73. http://www.ncbi.nlm.nih.gov/pubmed/8632490
3. Fowler FJ Jr, Barry MJ, Lu-Yao GL, et al. Patient-reported complications and follow-up treatment after radical prostatectomy. The National Medicare Experience: 1988-1990 (updated June 1993). Urology 1993;42(6):622-9. http://www.ncbi.nlm.nih.gov/pubmed/8256394
4. Partin AW, Pearson JD, Landis PK, et al. Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. Urology 1994;43(5): 649-59. http://www.ncbi.nlm.nih.gov/pubmed/7513108
5. Bott SRJ. Management of recurrent disease after radical prostatectomy. Prostate Cancer Prostatic Dis 2004;7(3):211-6. http://www.ncbi.nlm.nih.gov/pubmed/15278094
6. Polascik TJ, Oesterling JE, Partin AW. Prostate specific antigen: a decade of discovery - what we have learned and where we are going. J Urol 1999;162(2):293-306. http://www.ncbi.nlm.nih.gov/pubmed/10411025

7. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281(17):1591-7.
http://www.ncbi.nlm.nih.gov/pubmed/10235151
8. Moul JW. Prostate specific antigen only progression of prostate cancer. J Urol 2000;163(6):1632-42.
http://www.ncbi.nlm.nih.gov/pubmed/10799151
9. Amling CL, Bergstralh EJ, Blute ML, et al. Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? J Urol 2001; 165(4):1146-51.
http://www.ncbi.nlm.nih.gov/pubmed/11257657
10. Stephenson AJ, Kattan MW, Eastham JA, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. J Clin Oncol 2006; 24(24): 3973 -78.
http://www.ncbi.nlm.nih.gov/pubmed/16921049
11. American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statement: guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys 1997;37(5):1035-41.
http://www.ncbi.nlm.nih.gov/pubmed/9169810
12. Roach M 3rd, Hanks G, Thames H Jr, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006; 65:965-74.
http://www.mdconsult.com/das/citation/body/1206748702/jorg=journal&source=MI&sp=16362265&sid=0/N/16362265/1.html
13. Kapadia NS, Olson K, Sandler HM, et al. Interval to biochemical failure as a biomarker for cause-specific and overall survival after dose-escalated external beam radiation therapy for prostate cancer. Cancer 2012 Apr;118(8):2059-68.
http://www.ncbi.nlm.nih.gov/pubmed/22009287
14. Trapasso JG, deKernion JB, Smith RB, et al. The incidence and significance of detectable levels of serum prostate specific antigen after radical prostatectomy. J Urol 1994;152(5 Pt 2):1821-5.
http://www.ncbi.nlm.nih.gov/pubmed/7523728
15. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005 Jul;294(4):433-9.
http://www.ncbi.nlm.nih.gov/pubmed/16046649
16. Taylor JM, Griffith KA, Sandler HM. Definitions of biochemical failure in prostate cancer following radiation therapy. Int J Radiat Oncol Biol Phys 2001;50(5):1212-9.
http://www.ncbi.nlm.nih.gov/pubmed/11483331
17. Shen S, Lepor H, Yaffee R, et al. Ultrasensitive serum prostate specific antigen nadir accurately predicts the risk of early relapse after radical prostatectomy. J Urol 2005 Mar;173(3):777-80.
http://www.ncbi.nlm.nih.gov/pubmed/15711268
18. Boorjian SA, Thompson RH, Tollefson MK, et al. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. Eur Urol 2011 Jun;59(6):893-9.
http://www.ncbi.nlm.nih.gov/pubmed/21388736
19. Cher ML, Bianco FJ Jr, Lam JS, et al. Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. J Urol 1998;160(4):1387-91.
http://www.ncbi.nlm.nih.gov/pubmed/9751361
20. Kane CJ, Amling CL, Johnstone PAS, et al. Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. Urology 2003;61(3):607-11.
http://www.ncbi.nlm.nih.gov/pubmed/12639656
21. Gomez P, Manoharan M, Kim SS, et al. Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated? BJU Int 2004;94(3):299-302.
http://www.ncbi.nlm.nih.gov/pubmed/15291855
22. Johnstone PAS, Tarman GJ, Riffenburgh R, et al. Yield of imaging and scintigraphy assessing biochemical failure in prostate cancer patients. Urol Oncol 1997;3(4)108-14.
http://www.ncbi.nlm.nih.gov/pubmed/21227114
23. Cirillo S, Petracchini M, Scotti L, et al. Endorectal magnetic resonance imaging at 1.5 Tesla to assess local recurrence following radical prostatectomy using T2-weighted and contrast-enhanced imaging. Eur Radiol 2009; 19(3):761-9.
http://www.ncbi.nlm.nih.gov/pubmed/18825386
24. Kotzerke J, Volkmer BG, Neumaier B, et al. Carbon-11 acetate positron emission tomography can detect local recurrence of prostate cancer. Eur J Nucl Med Mol Imaging 2002 Oct;29(10):1380-4.
http://www.ncbi.nlm.nih.gov/pubmed/12271422

25. Cimitan M, Bortolus R, Morassut S, et al. [18F]fluorocholine PET/CT imaging for the detection of recurrent prostate cancer at PSA relapse: experience in 100 consecutive patients. Eur J Nucl Med Mol Imaging 2006 Dec;33(12):1387-98.
http://www.ncbi.nlm.nih.gov/pubmed/16865395
26. Fuccio C, Castellucci P, Schiavina R, et al. Role of 11C-choline PET/CT in the re-staging of prostate cancer patients with biochemical relapse and negative results at bone scintigraphy. Eur J Radiol 2012 Aug;81(8):e893-6.
http://www.ncbi.nlm.nih.gov/pubmed/22621862
27. Giovacchini G, Picchio M, Parra RG, et al. Prostate-specific antigen velocity versus prostate-specific antigen doubling time for prediction of 11C choline PET/CT in prostate cancer patients with biochemical failure after radical prostatectomy. Clin Nucl Med 2012 Apr;37(4):325-31.
http://www.ncbi.nlm.nih.gov/pubmed/22391699
28. Vees H, Buchegger F, Albrecht S, et al. 18F-choline and/or 11C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy. BJU Int 2007 Jun;99(6):1415-20.
http://www.ncbi.nlm.nih.gov/pubmed/17428249
29. Pelosi E, Arena V, Skanjeti A, et al. Role of whole-body 18F-choline PET/CT in disease detection in patients with biochemical relapse after radical treatment for prostate cancer. Radiol Med 2008 Sep;113(6):895-904. [Article in English, Italian]
http://www.ncbi.nlm.nih.gov/pubmed/18414809
30. Husarik DB, Miralbell R, Dubs M, et al. Evaluation of [(18)F]-choline PET/CT for staging and restaging of prostate cancer. Eur J Nucl Med Mol Imaging 2008 Feb;35(2):253-63.
http://www.ncbi.nlm.nih.gov/pubmed/17926036
31. Rinnab L, Mottaghy FM, Simon J, et al. [11C]Choline PET/CT for targeted salvage lymph node dissection in patients with biochemical recurrence after primary curative therapy for prostate cancer. Preliminary results of a prospective study. Urol Int 2008;81(2):191-7.
http://www.ncbi.nlm.nih.gov/pubmed/18758218
32. Krause BJ, Souvatzoglou M, Tuncel M, et al. The detection rate of [11C]Choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. Eur J Nucl Med Mol Imaging 2008 Jan;35(1):18-23.
http://www.ncbi.nlm.nih.gov/pubmed/17891394
33. Castellucci P, Fuccio C, Nanni C, et al. Influence of trigger PSA and PSA kinetics on 11C-Choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. J Nucl Med 2009 Sep; 50(9):1394-400.
http://www.ncbi.nlm.nih.gov/pubmed/19690023
34. Giovacchini G, Picchio M, Briganti A, et al. [11C]choline positron emission tomography/computerized tomography to restage prostate cancer cases with biochemical failure after radical prostatectomy and no disease evidence on conventional imaging. J Urol 2010 Sep;184(3):938-43.
http://www.ncbi.nlm.nih.gov/pubmed/20643445
35. Graute V, Jansen N, Ubleis C, et al. Relationship between PSA kinetics and [18F]fluorocholine PET/CT detection rates of recurrence in patients with prostate cancer after total prostatectomy. Eur J Nucl Med Mol Imaging 2012 Feb;39(2):271-82.
http://www.ncbi.nlm.nih.gov/pubmed/22086143
36. Beheshti M, Vali R, Waldenberger P, et al. The use of F-18 choline PET in the assessment of bone metastases in prostate cancer: correlation with morphological changes on CT. Mol Imaging Biol 2009 Nov-Dec;11(6):446-54.
http://www.ncbi.nlm.nih.gov/pubmed/19326171
37. Beheshti M, Vali R, Waldenberger P, et al. Detection of bone metastases in patients with prostate cancer by 18F fluorocholine and 18F fluoride PET-CT: a comparative study. Eur J Nucl Med Mol Imaging 2008 Oct;35(10):1766-74.
http://www.ncbi.nlm.nih.gov/pubmed/18465129
38. Giovacchini G, Picchio M, Coradeschi E, et al. Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging 2010 Feb;37(2):301-9.
http://www.ncbi.nlm.nih.gov/pubmed/19756592
39. Picchio M, Briganti A, Fanti S, et al. The role of choline positron emission tomography/computed tomography in the management of patients with prostate-specific antigen progression after radical treatment of prostate cancer. Eur Urol 2011 Jan;59(1):51-60.
http://www.ncbi.nlm.nih.gov/pubmed/20869161

40. Panebianco V, Sciarra A, Lisi D, et al. Prostate cancer: ^{1}HMRS-DCEMR at 3T versus [(18)F]choline PET/CT in the detection of local prostate cancer recurrence in men with biochemical progression after radical retropubic prostatectomy (RRP). Eur J Radiol 2012 Apr;81(4):700-8.
http://www.ncbi.nlm.nih.gov/pubmed/21330082
41. Heidenreich A, Semrau R, Thüer D, et al. Radical salvage prostatectomy: Treatment of local recurrence of prostate cancer after radiotherapy. Urologe A 2008 Nov;47(11):1441-6.
http://www.ncbi.nlm.nih.gov/pubmed/18806991
42. Schilling D, Schlemmer HP, Wagner PH, et al. Histological verification of 11C-choline-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. BJU Int Aug 2008;102(4):446-51.
http://www.ncbi.nlm.nih.gov/pubmed/18410442
43. Reske SN, Blumstein NM, Glatting G. [11C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. Eur J Nucl Med Mol Imaging 2008 Jan;35(1):9-17.
http://www.ncbi.nlm.nih.gov/pubmed/17828534
44. Pucar D, Shukla-Dave A, Hricak H, et al. Prostate cancer: correlation of MR imaging and MR spectroscopy with pathologic findings after radiation therapy-initial experience. Radiology 2005 Aug;236(2):545-53.
http://www.ncbi.nlm.nih.gov/pubmed/15972335
45. Rouvière O, Valette O, Grivolat S, et al. Recurrent prostate cancer after external beam radiotherapy: value of contrast-enhanced dynamic MRI in localizing intraprostatic tumor--correlation with biopsy findings. Urology 2004 May;63(5):922-7.
http://www.ncbi.nlm.nih.gov/pubmed/15134982
46. Thompson IM Jr, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006 Nov;296:2329-35.
http://www.ncbi.nlm.nih.gov/pubmed/17105795
47. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012 Dec;380(9858):2018-27.
http://www.ncbi.nlm.nih.gov/pubmed/23084481
48. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009 Mar;181:956-62.
http://www.ncbi.nlm.nih.gov/pubmed/19167731
49. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009 Jun;27:2924-30.
http://www.ncbi.nlm.nih.gov/pubmed/19433689
50. Cotter SE, Chen MH, Moul JW, et al. Salvage radiation in men after prostate-specific antigen failure and the risk of death. Cancer 2011 Sep;117(17):3925-32.
http://www.ncbi.nlm.nih.gov/pubmed/21437885
51. Siegmann A, Bottke D, Faehndrich J, et al. Salvage radiotherapy after prostatectomy - what is the best time to treat? Radiother Oncol 2012 May;103(2):239-43.
http://www.ncbi.nlm.nih.gov/pubmed/22119375
52. Ohri N, Dicker AP, Trabulsi EJ, et al. Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modelling. Eur J Cancer 2012 Apr;48(6):837-44.
http://www.ncbi.nlm.nih.gov/pubmed/21945099
53. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007 May;25(15):2035-41
http://www.ncbi.nlm.nih.gov/pubmed/17513807
54. Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatrment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. J Clin Oncol 2007 Jun;25(16):222-9.
http://www.ncbi.nlm.nih.gov/pubmed/17538167
55. Trabulsi EJ, Valicenti RK, Hanlon AL, et al. A multi-institutional matched-control analysis of adjuvant and salvage postoperative radiation therapy for pT3-4N0 prostate cancer. Urology 2008 Dec;72(6): 1298-302; discussion 1302-4.
http://www.ncbi.nlm.nih.gov/pubmed/18672274

56. Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA 2008 Jun;299:2760-9.
http://www.ncbi.nlm.nih.gov/pubmed/18560003
57. King CR, Spiotto MT. Improved outcomes with higher doses for salvage radiotherapy after prostatectomy. Int J Radiat Oncol Biol Phys 2008 May;71:23-7.
http://www.ncbi.nlm.nih.gov/pubmed/18207668
58. King CR, Kapp DS. Radiotherapy after prostatectomy: is the evidence for dose escalation out there? Int J Radiat Oncol Biol Phys 2008 Jun;71:346-50.
http://www.ncbi.nlm.nih.gov/pubmed/18234451
59. Schiffner DC, Gottschalk AR, Lometti M, et al. Daily electronic portal imaging of implanted gold seed fiducials in patients undergoing radiotherapy after radical prostatectomy. Int J Radiat Oncol Biol Phys 2007 Feb;67:610-9.
http://www.ncbi.nlm.nih.gov/pubmed/17236978
60. Mitchell DM, Perry L, Smith S, et al. Assessing the effect of a contouring protocol on postprostatectomy radiotherapy clinical target volumes and interphysician variation. Int J Radiat Oncol Biol Phys 2009 Nov;75:990-3.
http://www.ncbi.nlm.nih.gov/pubmed/19345515
61. Wiltshire KL, Brock KK, Haider MA, et al. Anatomic boundaries of the clinical target volume (prostate bed) after radical prostatectomy. Int J Radiat Oncol Biol Phys 2007 Nov 15;69(4):1090-9.
http://www.ncbi.nlm.nih.gov/pubmed/17967303
62. Poortmans P, Bossi A, Vandeputte K, et al. Guidelines for target volume definition in postoperative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. Radiother Oncol 2007 Aug;84:121-7.
http://www.ncbi.nlm.nih.gov/pubmed/17706307
63. Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med 1999 Dec;341:1781-8.
http://www.ncbi.nlm.nih.gov/pubmed/10588962
64. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006 Jun;7:472-9.
http://www.ncbi.nlm.nih.gov/pubmed/16750497
65. [No authors listed] The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initials results of the Medical Research Council Trial. Br J Urol 1997;79:235-46.
http://www.ncbi.nlm.nih.gov/pubmed/9052476
66. Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006 Apr;24:1868-76.
http://www.ncbi.nlm.nih.gov/pubmed/16622261
67. Mydin AR, Dunne MT, Finn MA, et al. Early salvage hormonal therapy for biochemical failure improved survival in prostate cancer patients after neoadjuvant hormonal therapy plus radiation therapy-a secondary analysis of irish clinical oncology research group 97-01. Int J Radiat Oncol Biol Phys 2013 Jan;85(1):101-8.
http://www.ncbi.nlm.nih.gov/pubmed/22658512
68. McLeod DG, Iversen P, See WA, et al. Bicalutamide 150mg plus standard care vs standard care alone for early prostate cancer. BJU Int 2006 Feb;97:247-54.
http://www.ncbi.nlm.nih.gov/pubmed/16430622
69. Zincke H, Lau W, Bergstralh E, et al. Role of early adjuvant hormonal therapy after radical prostatectomy for prostate cancer. J Urol 2001 Dec;166:2208-15.
http://www.ncbi.nlm.nih.gov/pubmed/11696737
70. Seay TM, Blute ML, Zincke H. Long-term outcome in patients with pTx N+ adenocarcinoma of prostate treated with radical prostatectomy and early androgen ablation. J Urol 1998 Feb;159:357-64.
http://www.ncbi.nlm.nih.gov/pubmed/9649239
71. Cheng L, Zincke H, Blute ML, et al. Risk of prostate carcinoma death in patients with lymph node metastasis. Cancer 2001 Jan;91:66-73.
http://www.ncbi.nlm.nih.gov/pubmed/11148561

72. Boorjian SA, Thompson RH, Siddiqui S, et al. Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. J Urol 2007 Sep;178 (3 Part 1):864-70; discussion 870-1.
http://www.ncbi.nlm.nih.gov/pubmed/17631342
73. Spiess PE, Lee AK, Busby JE, et al. Surgically managed lymph node-positive prostate cancer: does delaying hormonal therapy worsen the outcome? BJU Int 2007 Feb;99:321-5.
http://www.ncbi.nlm.nih.gov/pubmed/17155975
74. Wong YN, Freedland S, Egleston B, et al. Role of androgen deprivation therapy for node-positive prostate cancer. J Clin Oncol 2009 Jan;27:100-5.
http://www.ncbi.nlm.nih.gov/pubmed/19047295
75. Moul JW, Wu H, Sun L, et al. Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. J Urol 2004 Mar;171:1141-7.
http://www.ncbi.nlm.nih.gov/pubmed/14767288
76. Siddiqui SA, Boorjian SA, Inman B, et al. Timing of androgen deprivation therapy and its impact on survival after radical prostatectomy: a matched cohort study. J Urol 2008 May;179:1830-7; discussion 1837.
http://www.ncbi.nlm.nih.gov/pubmed/18353378
77. Makarov DV, Humphreys EB, Mangold LA, et al. The natural history of men treated with deferred androgen deprivation therapy in whom metastatic prostate cancer developed following radical prostatectomy. J Urol 2008 Jan;179:156-61; discussion 161-2.
http://www.ncbi.nlm.nih.gov/pubmed/18001801
78. Wirth M, Tyrrell C, Wallace M, et al. Bicalutamide (Casodex) 150 mg as immediate therapy in patients with localized or locally advanced prostate cancer significantly reduces the risk of disease progression. Urology 2001 Aug;58(2):146-51.
http://www.ncbi.nlm.nih.gov/pubmed/11489683
79. Wirth M. Delaying/reducing the risk of clinical tumour progression after primary curative procedures. Eur Urol 2001;40(Suppl 2):17-23.
http://www.ncbi.nlm.nih.gov/pubmed/11684860
80. Conti PD, Atallah AN, Arruda H, et al. Intermittent versus continuous androgen suppression for prostatic cancer. Cochrane Database Syst Rev 2007 Oct;(4):CD005009.
http://www.ncbi.nlm.nih.gov/pubmed/17943832
81. Goldenberg SL, Gleave ME, Taylor D, et al. Clinical experience with intermittent androgen suppression in prostate cancer: minimum of 3 years' follow-up. Mol Urol 1999;3(3):287-92.
http://www.ncbi.nlm.nih.gov/pubmed/10851335
82. Higano CS, Ellis W, Russell K, et al. Intermittent androgen suppression with leuprolide and flutamide for prostate cancer: a pilot study. Urology 1996 Nov;48(5):800-4.
http://www.ncbi.nlm.nih.gov/pubmed/8911533
83. Tunn UW. Intermittent endocrine therapy of prostate cancer. Eur Urol 1996;30(Suppl 1):22-5, discussion 38-9.
http://www.ncbi.nlm.nih.gov/pubmed/8977986
84. Grossfeld GD, Small EJ, Carroll PR. Intermittent androgen deprivation for clinically localized prostate cancer: initial experience. Urology 1998 Jan;51(1):137-44.
http://www.ncbi.nlm.nih.gov/pubmed/9457309
85. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med 2012 Sep;367(10):895-903.
http://www.ncbi.nlm.nih.gov/pubmed/22931259
86. Ziada AM, Crawford ED. Advanced prostate cancer. Prostate Cancer Prostatic Dis 1999 Jan;2(S1):21-6.
http://www.ncbi.nlm.nih.gov/pubmed/12496853
87. Harding P, Moul JW, McLeod DG. Combination flutamide and finasteride in PSA-only recurrence after prior local prostate cancer therapy. J Urol 1998;159(Suppl):130 (abstr).
88. Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy: observation in men with biochemical recurrence after radical prostatectomy. JAMA 2008 Jun; 299:2760-9.
http://www.ncbi.nlm.nih.gov/pubmed/18560003
89. Pearce A, Choo R, Danjoux C, et al. Effect of combined treatment with salvage radiotherapy plus androgen suppression on quality of life in patients with recurrent prostate cancer after radical prostatectomy. Int J Radiat Oncol Biol Phys 2006 May;65:78-83.
http://www.ncbi.nlm.nih.gov/pubmed/16563657

90. Parker C, Clarke N, Logue J, et al. RADICALS (Radiotherapy and Androgen Deprivation inCombination after Local Surgery). Clin Oncol (R Coll Radiol) 2007 Apr;19:167-71.
http://www.ncbi.nlm.nih.gov/pubmed/17359901
91. Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol 2008 Jan;53:68-80.
http://www.ncbi.nlm.nih.gov/pubmed/17920184
92. Grossfeld GD, Li YP, Lubeck DP, et al. Predictors of secondary cancer treatment in patients receiving local therapy for prostate cancer: data from cancer of the prostate strategic urologic research endeavor. J Urol 2002 Aug;168(2):530-5.
http://www.ncbi.nlm.nih.gov/pubmed/12131303
93. Ahlering TE, Lieskovsky G, Skinner DG. Salvage surgery plus androgen deprivation for radioresistant prostatic carcinoma. J Urol 1992 Mar;147(3 Pt 2):900-2.
http://www.ncbi.nlm.nih.gov/pubmed/1538492
94. Zincke H. Radical prostatectomy and exenterative procedures for local failure after radiotherapy with curative intent: comparison of outcomes. J Urol 1992 Mar;147(3 Pt 2):894-9.
http://www.ncbi.nlm.nih.gov/pubmed/1538491
95. Lerner SE, Blute ML, Zincke H. Critical evaluation of salvage surgery for radio-recurrent/resistant prostate cancer. J Urol 1995 Sep;154(3):1103-9.
http://www.ncbi.nlm.nih.gov/pubmed/7543608
96. Rogers E, Ohori M, Kassabian S, et al. Salvage radical prostatectomy: outcome measured by serum prostate specific antigen levels. J Urol 1995 Jan;153(1):104-10.
http://www.ncbi.nlm.nih.gov/pubmed/7526002
97. Garzotto M, Wajsman Z. Androgen deprivation with salvage surgery for radiorecurrent prostate cancer: result of a 5-year follow-up. J Urol 1998 Mar;159(3):950-4;discussion 954-5.
http://www.ncbi.nlm.nih.gov/pubmed/9474190
98. Vaidya A, Soloway MS. Salvage radical prostatectomy for radiorecurrent prostate cancer: morbidity revisited. J Urol 2000 Dec;164(6):1998-2001.
http://www.ncbi.nlm.nih.gov/pubmed/11061900
99. Stephenson AJ, Scardino PT, Bianco FJ, et al. Morbidity and functional outcomes of salvage radical prostatectomy for locally recurrent prostate cancer after radiation therapy. J Urol 2004 Dec;172 (6 Pt 1):2239-43.
http://www.ncbi.nlm.nih.gov/pubmed/15538239
100. Heidenreich A, Ohlmann C, Ozgür E, et al. [Functional and oncological outcome of salvage prostatectomy of locally recurrent prostate cancer following radiation therapy] Urologe A 2006 Apr; 45(4):474-81. [Article in German]
http://www.ncbi.nlm.nih.gov/pubmed/16465521
101. Heidenreich A, Richter S, Thüer D, et al. Prognostic parameters, complications, and oncologic and functional outcome of salvage radical prostatectomy for locally recurrent prostate cancer after 21st-century radiotherapy. Eur Urol 2010 Mar;57(3):437-43.
http://www.ncbi.nlm.nih.gov/pubmed/19303197
102. Chade DC, Eastham J, Graefen M, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. Eur Urol 2012 May;61(5):961-71.
http://www.ncbi.nlm.nih.gov/pubmed/22280856
103. Chade DC, Shariat SF, Cronin AM, et al. Salvage radical prostatectomy for radiation-recurrent prostate cancer: a multi-institutional collaboration. Eur Urol 2011 Aug;60(2):205-10.
http://www.ncbi.nlm.nih.gov/pubmed/21420229
104. Ahallal Y, Shariat SF, Chade DC, et al. Pilot study of salvage laparoscopic prostatectomy for the treatment of recurrent prostate cancer. BJU Int 2011 Sep;108(5):724-8.
http://www.ncbi.nlm.nih.gov/pubmed/21166755
105. Rocco B, Cozzi G, Spinelli MG, et al. Current status of salvage robot-assisted laparoscopic prostatectomy for radiorecurrent prostate cancer. Curr Urol Rep 2012 Jun;13(3):195-201.
http://www.ncbi.nlm.nih.gov/pubmed/22430278
106. Mouraviev V, Spiess PE, Jones JS. Salvage cryoablation for locally recurrent prostate cancer following primary radiotherapy. Eur Urol 2012 Jun;61(6):1204-11.
http://www.ncbi.nlm.nih.gov/pubmed/22421081
107. Cespedes RD, Pisters LL, von Eschenbach AC, et al. Long-term follow-up of incontinence and obstruction after salvage cryosurgical ablation of the prostate: results in 143 patients. J Urol 1997 Jan;157(1):237-40.
http://www.ncbi.nlm.nih.gov/pubmed/8976261

108. Ismail M, Ahmed S, Kastner C, Davies J. Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. BJU Int 2007 Oct;100(4):760-4. http://www.ncbi.nlm.nih.gov/pubmed/17662081
109. Pisters LL, Rewcastle JC, Donnelly BJ, et al. Salvage prostate cryoablation: initial results from the cryo on-line data registry. J Urol 2008 Aug;180(2):559-63. http://www.ncbi.nlm.nih.gov/pubmed/18554664
110. Pisters LL, Leibovici D, Blute M, et al. Locally recurrent prostate cancer after initial radiation therapy: a comparison of salvage radical prostatectomy versus cryotherapy. J Urol 2009 Aug;182(2):517-25; discussion 525-7. http://www.ncbi.nlm.nih.gov/pubmed/19524984
111. Jo Y, Fujii T, Hara R, Yokoyama T, et al. Salvage high-dose-rate brachytherapy for local prostate cancer recurrence after radiotherapy - preliminary results. BJU Int 2012 Mar;109(6):835-9. http://www.ncbi.nlm.nih.gov/pubmed/21933327
112. Beyer DC. Permanent brachytherapy as salvage treatment for recurrent prostate cancer. Urology 1999 Nov;54(5):880-3. http://www.ncbi.nlm.nih.gov/pubmed/10565751
113. Gomez-Veiga F, Mariño A, Alvarez L, et al. Brachytherapy for the treatment of recurrent prostate cancer after radiotherapy or radical prostatectomy. BJU Int 2012 Feb;109 Suppl 1:17-21. http://www.ncbi.nlm.nih.gov/pubmed/22239225
114. Moman MR, van der Poel HG, Battermann JJ, et al. Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy. Brachytherapy 2010 Apr-Jun;9(2):119-25. http://www.ncbi.nlm.nih.gov/pubmed/19850536
115. Pinover WH, Horwitz EM, Hanlon AL, et al. Validation of a treatment policy for patients with prostate specific antigen failure after three-dimensional conformal prostate radiation therapy. Cancer 2003 Feb;97(4):1127-33. http://www.ncbi.nlm.nih.gov/pubmed/12569615
116. Zacharakis E, Ahmed HU, Ishaq A, et al. The feasibility and safety of high-intensity focused ultrasound as salvage therapy for recurrent prostate cancer following external beam radiotherapy. BJU Int 2008 Sep;102(7):786-92. http://www.ncbi.nlm.nih.gov/pubmed/18564135
117. Murat FJ, Poissonnier L, Rabilloud M, et al. Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. Eur Urol 2009 Mar;55(3):640-7. http://www.ncbi.nlm.nih.gov/pubmed/18508188
118. Ahmed HU, Ishaq A, Zacharakis E, et al. Rectal fistulae after salvage high-intensity focused ultrasound for recurrent prostate cancer after combined brachytherapy and external beam radiotherapy. BJU Int 2009 Feb;103(3):321-3. http://www.ncbi.nlm.nih.gov/pubmed/19021611

20. CASTRATION-RESISTANT PCA (CRPC)

20.1 Background

Cancer of the prostate is a heterogeneous disease. Our knowledge of the mechanisms involved in androgen-independent prostate cancer, which is now known as castration-resistant prostate cancer (CRPC), remains incomplete, but is starting to become clearer (1,2). An alteration in normal androgen signalling is thought to be central to the pathogenesis of CRPC (3). It is mediated through two main, overlapping, mechanisms, which are androgen-receptor (AR)-independent and AR-dependent.

*20.1.1 **Androgen-receptor-independent mechanisms***

Androgen-receptor-independent mechanisms may be associated with the deregulation of apoptosis through the deregulation of oncogenes. High levels of bcl-2 expression are seen with greater frequency as PCa progresses. The regulation of microtubule integrity may be a mechanism through which bcl-2 induces its anti-apoptotic effect (4,5). Indeed, most drugs that are active in CRPC work by inhibiting microtubule formation. The tumour suppressor gene p53 is more frequently mutated in CRPC. Overexpression of bcl-2 and p53 in prostatectomy specimens has been shown to predict an aggressive clinical course (6,7). Clinical trials are underway to target the bcl-2 pathway (8), and the MDM2 (mouse double minute 2) oncogene (9) and the PTEN

(phosphatase and tensin homolog) suppressor gene may also be involved (10).

*20.1.2 **Androgen-receptor-dependent mechanisms***

Direct AR-dependent mechanisms comprise the main pathway. Ligand-independent androgen receptor (AR) activation has been suspected, such as the tyrosine-kinase-activated pathway [insulin-like growth factor-1, keratinocyte growth factor, and epidermal growth factor (EGF)]. EGF is a potent mitogen of prostate stromal and epithelial cells. It is produced in high levels locally and acts as a paracrine stimulator. In AR-independent tumours, autocrine stimulation may become more important, which could allow unregulated growth.

Androgen receptor amplification and overexpression are observed in one-third of CRPC tissues (11,12) and may lead to AR hypersensitivity. Androgen receptor mutations may lead to a functional change in receptor function (13). At the same time, there is an intracellular increase in androgens from in-situ conversion (14,15). This increase may be secondary to an increase in the enzymes involved in intracellular androgen synthesis (16).

Androgen receptor mutations are found in only a subpopulation of tumour cells, therefore, they are unlikely to be responsible for the entire spectrum of the AR-independent state (17). The AR mutations might be related to the selective pressure of anti-androgens (17). The recent discovery of gene fusion between the androgen-driven TMPRSS2 and the EGR-ETS oncogene family (18) raises the question of oncogene regulation through androgen regulation pathways. In gene fusion, an androgen-responsive element from an androgene-regulated gene becomes associated with genes that are usually not androgen-regulated, so that they too become subject to androgen regulation. Currently, their implication in CRPC is hypothetical. Even in castrated patients, metastatic tissues have repeatedly shown high levels of androgens, suggesting a high level of intracrine synthesis (16,19). It is possible that a high intraprostatic cholesterol level can activate specific androgen pathways (20).

20.2 Definition of relapsing prostate cancer after castration

The precise definition of recurrent or relapsed PCa remains controversial and several groups have published practical recommendations for defining CRPC (19,20).

Various different terms have been used to describe PCa that relapses after initial hormonal ablation therapy, including hormone-refractory PCa, androgen-independent cancer and hormone-independent cancers. In recent years, the term CRPC has become more frequently used than hormone refractory or androgen- independent PCa. This is based predominantly on recent findings suggesting that advancing PCa is not uniformly refractory to further hormonal manipulation and that androgens and disease progression are frequently dependent on androgen receptor interactions. Castration-resistant prostate cancer, which is still hormone sensitive, has been clearly characterised, with new drugs targeting the AR, such as MDV3100 (Enzalutamide), or androgen synthesis, via CYP 17 inhibition, such as abiraterone acetate or TAK700 (21). Table 21 lists the key defining factors of CRPC.

Table 21: Definition of CRPC

Castrate serum levels of testosterone < 50 ng/dL or < 1.7 nmol/L.
Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL.
Anti-androgen withdrawal for at least 4 weeks for flutamide and for at least 6 weeks for bicalutamide*
PSA progression, despite consecutive standard hormonal manipulations†

** Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done to fulfil the criteria for CRPC if patients have been treated with anti-androgens in the context of maximum androgen blockade or step-up therapy following PSA progression after failure of LHRH treatment.*

† Progression or appearance of two or more bone lesions on bone scan or soft tissue lesions using RECIST (Response Evaluation Criteria in Solid Tumours) with nodes ≥ 2 cm in diameter.

20.3 Assessing treatment outcome in CRPC

In general, the therapeutic outcome should be assessed using the guidelines for the evaluation of treatment response in solid tumours, recently published by the RECIST group (Response Evaluation Criteria In Solid Tumours) (22). However, 80-90% of patients do not have bi-dimensionally measurable disease. Patients with primarily soft tissue cancers often have a different prognosis to those with only bone metastases. Osteoblastic bone metastases remain difficult to quantify accurately. Magnetic resonance imaging (MRI) might be useful for assessing axial metastases (23). The cause of death in PCa patients is often unreliable, therefore a more valid end-point might be OS rather than a disease-specific one (24).

20.3.1 ***PSA level as marker of response***

Many contemporary studies use PSA as a marker of response, even though there is no consensus about the magnitude and duration of a decline in PSA level. Although PSA is used as a rapid screening tool to test the activity of new agents, there is conflicting evidence about the role of PSA as a response marker. Trials of the vaccines sipuleucel-T (Provenge) (25) and TRICOM (PROSTVAC) (26) have demonstrated a significant OS benefit without any PSA change, raising questions about the value of PSA response for non-hormonal non-cytotoxic drugs (27).

In addition, wide fluctuations have been seen in PSA values due to a transient effect of drugs on PSA production. The effect of drugs on PSA expression should be considered when interpreting PSA response data, which should be viewed together with other clinical data (28-35).

Nevertheless, it has been shown reproducibly that ≥ 50% PSA decline in pre-treatment PSA following therapy carries a significant survival advantage (36,37).

An improved PSA response was also associated with prolonged survival in the TAX 327 study, with a median survival of 33 months when the PSA was normalised (< 4 ng/mL) vs. 15.8 months for an abnormal PSA. This study also showed that a PSA response was not a surrogate marker for survival. Even though the same PSA response rate was found in both docetaxel arms (45%), improved survival only occurred with the 3-weekly docetaxel regimen. According to the most recent evaluation of the TAX 327 and SWOG 99-16 studies, a PSA detection of ≥ 30% is associated with a significant survival benefit (38,39).

20.3.2 ***Other parameters***

Evaluation of molecular markers is just beginning. The most frequently described and probably most interesting tool is the circulating tumour cell (CTC) count, which has been developed in parallel with abiraterone. The CTC count was related to survival in several trials (40-42) and might become a surrogate marker for survival. The Food and Drug Administration (FDA) has recently approved an assay for CTCs. In patients with symptomatic bone lesions, pain reduction or complete pain relief may be used as parameters to assess palliative therapeutic response (43). In a landmark analysis of TAX 327, PSA response and pain response, but not QoL response, were independently associated with survival (44).

20.3.3 ***Recommendations for assessing therapeutic response***

In everyday practice, the evaluation of treatment response must be based on symptom improvement, prolonged survival, or other pre-defined targets. The Prostate Cancer Working Group 2 (PCWG2) recommends that investigators measure early outcomes by the changes in the individual disease manifestations present initially for both cytotoxic and non-cytotoxic drugs with the same methods used at enrolment (19). If a protocol defines a composite end-point for progression, the specified progression in any measure (with the exception of early changes in PSA or pain) overrides a change or improvement in other measures.

Recommendations	**LE**	**GR**
For PSA, recognise that a favourable effect may be delayed for ≥ 12 weeks, even for a cytotoxic drug. Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks, unless there is other evidence of progression. Ignore early rises ≤ 12 weeks when determining PSA response.	1a	A
For bone disease; record outcome as new lesions or no new lesions. • First scheduled reassessment: no new lesions: continue therapy. • New lesions: perform a confirmatory scan ≥ 6 weeks later; confirmatory scan: no new lesions: continue therapy. • Additional new lesions: progression; subsequent scheduled reassessments: no new lesions: continue; new lesions: progression.		
In non-osseous metastases from CRPC, assessment should adhere to the RECIST criteria.	1b	A
In patients with advanced symptomatic metastatic CRPC, the therapeutic response can be best assessed by improvement of symptoms. Document pain and analgesia at entry with a lead-in period and measure repeatedly at 3-4 week intervals. Perform serial assessments of global changes in HRQoL, urinary or bowel compromise, pain management, and additional anticancer therapy. Ignore early changes (12 weeks) in pain or HRQoL in absence of compelling evidence of disease progression. Confirm response or progression of pain or HRQoL end-points 3 weeks later.	1b	A

CRPC = castration-resistant prostate cancer; HRQoL = health-related quality of life; PSA = prostate-specific antigen; RECIST = response evalutation criteria in solid tumours.

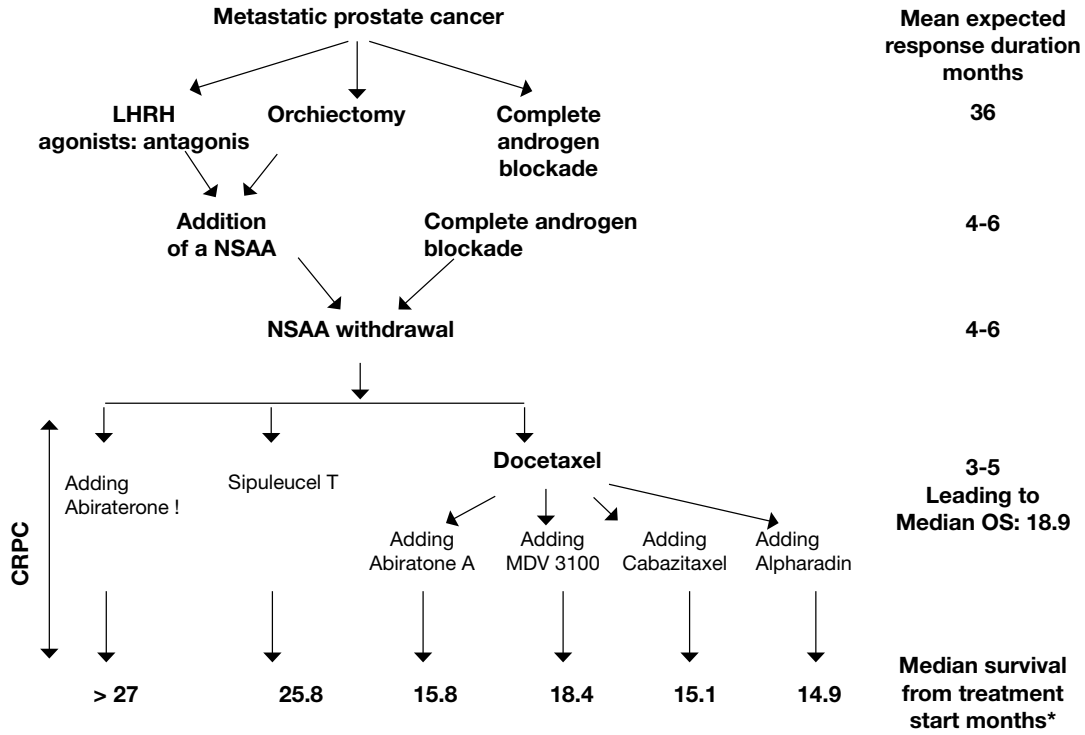
20.4 Androgen deprivation in castration-resistant PCa

The existence of androgen-resistant PCa shows that disease progression occurs despite castration. The castration levels of testosterone must therefore be documented and a serum testosterone level < 50 ng/dL (1.7 nmol/L) should be documented at initial relapse on hormonal therapy (45).
Continued testicular androgen suppression in CRPC has a minimal overall effect. The recommendation to continue ADT with LHRH analogues, despite PSA progression, is based on the data of Manni et al. (46). They demonstrated significantly lower survival rates in patients without complete androgen blockade (CAB). However, these data have been challenged by two trials that showed only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies (47,48).
However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. Androgen suppression should therefore be continued indefinitely in these patients.

20.5 Secondary hormonal therapy

For the patient with progressive disease after ADT, there are many therapeutic options. They include anti-androgen withdrawal, addition of anti-androgens, anti-androgen replacement, oestrogenic compounds, adrenolytic agents, and novel approaches (49). Figure 1 summarises the treatment modalities and expected responses.

Figure 1: Flowsheet of the potential therapeutic options after PSA progression following initial hormonal therapy



LHRH = luteinising hormone releasing hormone; Abiraterone A: abiraterone acetate
** Median cannot be compared because patients included in trials did not have the same characteristics*

20.6 Anti-androgen withdrawal syndrome

Anti-androgen withdrawal syndrome is a critical discovery in understanding the biology of androgen independence, interpreting clinical trials, and treating patients (50- 53).
Approximately one-third of patients respond to anti-androgen withdrawal, as indicated by a ≥ 50% PSA decrease, for a median duration of approximately 4 months. Anti-androgen withdrawal responses have also been reported with bicalutamide and megestrol acetate (54-59). Recently, in the SWOG 9426 trial, PSA progression despite CAB was reported in a subgroup of 210 patients with an M0 or M1 stage tumour (60). A response was observed in 21% of patients, even though there was no radiographic response. Median PFS was 3 months, with 19% (all M0) having PFS ≥ 12 months'. Increased PFS and OS were associated with longer use of non-steroidal drugs, lower PSA at baseline and M0-stage. These results were obtained with patients on CAB

following androgen withdrawal. No data were available on the withdrawal effect following second-line anti-androgen treatment.

In conclusion, androgen withdrawal must be systematically considered as a first-line modality in relapsing patients, even if its efficacy is limited (LE: 2).

20.7 Classical hormonal treatment alternatives after CRPC occurrence

Simple old fashion modalities have been reported, without any associated survival benefit ever reported.

20.7.1 ***Bicalutamide***

Bicalutamide has a dose response, with higher doses producing a greater reduction in PSA level (61). The largest cohort so far is based on 52 CRPC patients treated with 150 mg bicalutamide (62). A palliative effect was clear and a 20% PSA response (at least 50% decrease) was observed, without any link to the palliative effect. Based on the affinity of dihydrotestosterone for the AR, a large randomised trial (TARP) is ongoing comparing the effectiveness of 50 mg bicalutamide combined with either dutasteride or placebo in non-metastatic CRPC (63). The addition of a non-steroidal anti-androgen to gonadal suppression at the time of PSA failure appears to result in declining PSA in only a few patients (64,65).

20.7.2 ***Switching to an alternative anti-androgen therapy***

There has been recent interest in another simple modality, namely, the alternative anti-androgen therapy (66). After CAB was stopped in 232 patients with progressive disease (76% with stage M1b), a withdrawal effect was observed in 31 men (15.1%). Second-line hormonal treatment was performed by giving an alternative non-steroidal drug (i.e. initial flutamide was replaced by bicalutamide and vice versa). An overall > 50% decline in PSA was observed in 83 men (35.8%), irrespective of any previous withdrawal effect, which lasted > 6 months. The higher the PSA at the start of second-line therapy, the shorter was the FPS and the lower was the PSA response rate.

20.7.3 ***Anti-androgen withdrawal accompanied by simultaneous ketoconazole***

The adrenal glands secrete approximately 10% of circulating androgen in humans. This can be inhibited using aminoglutethimide, ketoconazole and corticosteroids (67-71) resulting in a PSA response in ~ 25% of patients of ~ 4 months duration. The simultaneous addition of ketoconazole to anti-androgen withdrawal, produced a significantly increased PSA response (32% vs. 11%) and a longer time to PSA progression (8.6 vs. 5.9 months) compared to anti-androgen withdrawal alone (71).

20.7.4 ***Oestrogens***

Prostate cancer usually expresses oestrogen receptors, which are upregulated after androgen ablation in animal models. Diethylstilboestrol (DES) (72-74) achieved a positive PSA response in 24% and 80% of patients, with an overall estimated survival of 63% at 2 years. However, even at low doses of DES, about one-third (31%) of patients developed deep venous thrombosis and 7% experienced myocardial infarction.

20.8 Novel hormonal drugs targeting the endocrine pathways

In the past 2 years, following early phase I/II trials in patients with CRPC, new compounds appeared for treating CRPC (Section 19.4). Most have been developed post docetaxel, but abiraterone acetate and MDV 3100 have been used before chemotherapy. The initial results have been recently published from the large phase III trial COU-AA-302, in which 1088 chemonaïve CRPC patients were randomised to abiraterone acetate and placebo, both combined with prednisone (75). Patients were diagnosed with CRPC according to the PCWG2 criteria, and were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and asymptomatic or mildly symptomatic. The study had two joint primary end-points: OS and radiographic PFS. The results reported are from the second preplanned interim analysis. After a median follow-up of 22 months, there was significant radiological PFS (median 16.5 vs. 8.3 months, HR: 0.53, P < 00.1 below the prespecified boundary). Regarding OS, there was a trend (median not reached vs. 27.2 months, HR: 0.75, P = 0.01). However, this value was above the prespecified P value for the second interim analysis (P < 0.001), leading to a non-significant difference. All the subgroup analyses and secondary end-points consistently favoured the abiraterone arm. Side effects related to mineralocorticoids and liver function were more frequent with abiraterone, but mostly grade 1/2. These positive results have led to European Medicines Agency (EMEA) drug approval but it must be emphasised that one of the primary end-points has not yet been reached, leading to an overall inconclusive result.

Regarding MDV3100, accrual for the phase III trial (PREVAIL) is complete but no results are available to date.

20.9 Non-hormonal therapy

Several chemotherapeutic options have been reported from phase III trials in CRPC (Table 22). Several trials

are underway, using different approaches through all the known pathways. A detailed review is far beyond the scope of these guidelines (1). Docetaxel is currently the standard of care.

*20.9.1 **Docetaxel regimen***

A significant improvement in median survival of 2-2.5 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy (76,77). In the SWOG 99-16 trial, pain relief was similar in both groups, although side effects occurred significantly more often with docetaxel than with mitoxantrone.
The standard for first-line cytotoxic chemotherapy is docetaxel using the same regimen as in the TAX 327 trial, that is, 75 mg/m^2 3 weekly combined with prednisone 5 mg BID, up to 10 cycles of survival, and palliation is the main target. The weekly regimen is not associated with improved survival and does not appear to be better tolerated.

The patients considered for docetaxel represent a heterogeneous population. Several poor prognostic factors have been described, such as a PSA level > 114 ng/mL, PSA doubling time (PSA-DT) < 55 days, or the presence of visceral metastases (78). A better risk group definition has been recently presented, based on the TAX 327 study cohort. The predictive factors were visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine before docetaxel. Patients were categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), leading to three different lengths of median OS: 25.7, 18.7 and 12.8 months, respectively (39). In addition, two independent studies have suggested that improved survival can be predicted by C-reactive protein (CRP) levels < 8 mg/L (HR, 2.96) (79,80). Age by itself is not a contraindication to docetaxel (81).

Table 22: PSA response rates, mean survival, time to progression, and pain reduction in the large, prospective, randomised phase III trials of chemotherapy in patients with CRPC

Study	n	PSA decrease > 50%	Decrease in pain	Survival (months)	Time to progression
TAX 327 (77)					
Mitoxantrone, 3 times weekly, 12 mg/m^2, Prednisone 5 mg BID		32%	22%	16.5	-
Docetaxel, 3 times weekly, 75 mg/m^2 prednisone 5 mg BID		45%	35%	18.91	-
Docetaxel, weekly, 30 mg/m^2 prednisone 5 mg BID		48%	31%	17.4	-
SWOG 99-16 (76)					
Mitoxantrone, 3 times weekly, 12 mg/m^2 prednisone 5 mg BID	336	50%	-	15.6	3.2 months
Docetaxel/EMP, 3 times weekly, 60 mg/m^2, EMP 3 x 280mg/day	338	27%	-	17.52	6.3 months
CALGB 9182 (82)					
Hydrocortisone	123	38%	-	12.3	2.3 months
Hydrocortisone					
Mitoxantrone/HC, 3 times times weekly, 12 mg/m^2	119	22%	-	12.6	3.7 months
Tannock et al. (83)					
Prednisone	81	22%	12%	-	18 weeks
Mitoxantrone/Pred, 3 times weekly, 12 mg/m^2	80	33%	29%	-	43 weeks

EMP = estramustine; HC = hydrocortisone; 1p < 0.000 compared to mitoxantrone; 2p = 0.001 compared to mitoxantrone.

*20.9.2 **Other classical regimen***

20.9.2.1 Mitoxantrone combined with corticosteroids

Mitoxantrone combined with corticosteroids (82,83) has been extensively studied; primarily in patients with symptomatic bone lesions due to CRPC. Palliation is effective with a clear PSA response and increased PFS, leading to a significant improvement in QoL, no survival benefit was ever observed.

20.9.2.2 Other chemotherapy regimen

The synergy observed for estramustine combined with other drugs that target microtubule action has generated promising results in prospective clinical trials. Combination with vinblastine is the most frequently studied

combination. Significant PSA and measurable responses have been reported, without any survival benefit (84). A recent meta-analysis (85) concluded that addition of estramustine to chemotherapy increased the time to PSA progression and OS. However, there was a significant increased risk (up to 7%) of thromboembolic events, (86), requiring systematic prevention with coumadin. Intravenous cyclophosphamide, or new oral formulations have been tested, without any clear survival benefit (87,88). Cisplatin and carboplatin have activity as single agents against PCa and have a synergistic effect, as with estramustine. Combination of estramustine, etoposide and cisplatin (or carboplatin) has significant activity against poorly differentiated CRPC. Combination of estramustine, etoposide and paclitaxel has high response rates (89,90). Preliminary results from phase II with alternative chemotherapy regimens have been reported (89,91-93), including pegylated doxorubicin, vinorelbine; a combination of paclitaxel, carboplatin and estramustine; combination of vinblastine, doxorubicin and radionuclides; and combination of docetaxel and mitoxantrone. The lack of large phase III trials and unknown long-term efficacy are major problems associated with all these studies. Therefore none of the above drugs are considered as clear valid options in CRPC.

20.9.3 ***Specific bone-targeted therapies***

Bone is a primary target for prostatic metastatic cells, which forms a rationale for bone-protective drugs that prevent cancer cells from colonising and developing in bone. Besides zoledronic acid and denosumab (see Section 12.7.1), other drugs, that specifically target the endothelin-1 axis have been tested. The first of these (atrasentan) resulted in clear biological responses, but questionable clinical results (94), possibly secondary to an inappropriate trial design. Second-generation blockers (zibotentan) have been tried in large phase III trials in metastatic and non-metastatic CRPC but finally stopped due to negative results in relation to OS (95).

The only bone-specific drug that is associated with a survival benefit is alpharadin, a radium 223 α-emitter. In the large phase III trial (ALSYMPCA) 921 patients with symptomatic CRPC, who failed or were unfit for docetaxel therapy, were randomised to six injections of 50 kBq/kg alpharadin or placebo. The primary end-point was OS. The results of this trial have been repeatedly presented but only partially published (96,97). Alpharadin significantly improved OS by 3.6 months. The associated toxicity was minimal, specially the hematologic one, and did not differ significantly from that in the placebo arm.

20.9.4 ***Vaccine***

In 2010, a phase III trial of Sipuleucel T showed a survival benefit in 512 CRPC patients (97). This was the first time that a PCa vaccine had shown a benefit and led to FDA approval and a submission to the EMEA. Sipuleucel T is an active cellular immunotherapy agent consisting of autologous peripheral blood mononuclear cells, activated in vitro by a recombinant fusion protein comprising prostatic acid phosphatase fused to granulocyte–macrophage colony-stimulating factor, which is an immune-cell activator. In the above trial, patients with metastatic CRPC, with PSA > 5 ng/mL, castrate testosterone level, and no visceral metastases, were randomised to three infusions 2 weeks apart with Sipuleucel T or placebo. Up to two previous chemotherapy regimens were allowed (effective in 19.6% Sipuleucel T treated patients and in 15.2% respectively). The main objective was OS. After a median follow-up of 34 months, the median survival was 25.8 months in the Sipuleucel T group compared to 21.7 months in the placebo group, leading to a significant HR of 0.78 (P = 0.03). Surprisingly, PFS was equivalent in both arms (14 weeks). The overall tolerance was acceptable, with more cytokine-related adverse events in the Sipuleucel T group but the same grade 3–4 in both arms. Apart from its availability, the major question related to Sipuleucel T is its cost.

20.10 How to choose the first “second line” treatment in CRPC

The timing of second-line treatment remains unclear in metastatic CRPC. Provided it is available, Sipuleucel T should probably be used early in the course of the disease. Until abiraterone acetate became available clinically, the discussion focused solely on when to start docetaxel therapy, after all the secondary classical hormonal manipulation had been undertaken.

It is advisable to start it immediately in symptomatic patients, if possible every 3 weeks, because this schedule is associated with an improvement in survival. However, a weekly regimen will result in the same symptom improvement and must be considered in patients unable to receive the optimal regimen (LE: 1b), as it is more effective than best supportive care (99). In asymptomatic patients, timing is not so clear and must be discussed individually.

The COU-AA-302 trial raises the question of prechemotherapy use of this new compound, and the possible selection criteria between second-line chemotherapy or hormonotherapy. Also some very preliminary retrospective observations might be helpful, it is so far impossible to predict which subset of patients is most likely to respond to one specific second-line treatment modality.

Finally, the only indication for chemotherapy in CRPC non-metastatic patients is inside clinical trials and patients should be advised to participate.

20.11 Salvage treatment after first- line docetaxel

All patients who receive docetaxel-based chemotherapy for CRPC will progress, thus, there have been many clinical trials investigating the role of salvage chemotherapy. Recently, there have been major improvements in this situation. Two treatment possibilities are now available: new hormonal treatment or new chemotherapy regimens. The results suggest that the most appropriate approaches are cabazitaxel (100), intermittent docetaxel chemotherapy (101,102), and potentially, molecular-targeted therapy (103,104).
Several groups have used second-line intermittent docetaxel in patients who had clearly responded to first-line docetaxel (101,102,105). In general, a PSA response can be achieved in about 60% of patients with a median time to progression of about 6 months, while treatment-associated toxicity is minimal and similar to that of first-line docetaxel. Another, recently identified approach is molecular-targeted therapy (103,106-108) although more research is needed in larger groups of patients.

Platinum-based chemotherapeutic regimes have been investigated in patients with CRPC. Although the platinum complex, satraplatin, has shown activity against CRPC and some promise in clinical trials, the FDA rejected it for CRPC in 2008 (104).

Many new drugs, such as gefitinib, bevacizumab (phase III trial CALB 90401 ongoing), oblimersen (phase II trial EORTC 30021), and also a vaccine, G-Vax (108), have been tested in phase II/III trials without any positive impact on the primary end-point. The G-VAx trial was stopped prematurely because of a significantly higher mortality in the treatment arm as compared to the docetaxel control arm.

20.11.1 ***Cabazitaxel***

Cabazitaxel is a taxane derivative with some significant differences compared to docetaxel. Positive results have been published from a large prospective, randomised, phase III trial (TROPIC trial) comparing cabazitaxel + prednisone vs. mitoxantrone + prednisone in 755 patients with CRPC, who had progressed after or during docetaxel-based chemotherapy (100). Patients received a maximum of 10 cycles of cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m^2) plus prednisone (10 mg/day), respectively. Overall survival was the primary end-point and PFS, treatment response and safety were secondary end-points. An OS benefit (15.1 vs. 12.7 months, $P < 0.0001$) was observed in the cabazitaxel arm. There was also a significant improvement in PFS (2.8 vs. 1.4 months, $P < 0.0001$), objective response rate according to RECIST criteria (14.4% vs. 4.4%, $P < 0.005$), and PSA response rate (39.2% vs. 17.8%, $P < 0.0002$). Treatment-associated WHO grade 3/4 side effects developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, $P < 0.0002$) and non-haematological (57.4% vs. 39.8%, $P < 0.0002$) toxicity (100). This drug should be administered by physicians with expertise in handling neutropenia and sepsis, possibly with granulocyte colony-stimulating factor.

20.11.2 ***Enzalutamide (MDV3100)***

Enzalutamide (formerly known as MDV3100) is a novel anti-androgen that blocks AR transfer to the nucleus, in contrast to currently available drugs with which AR is able to transfer to the nucleus. Enzalutamide is used as a once-daily oral treatment. The planned preliminary analysis of the AFFIRM study was published in 2012 (109). This trial randomised 1,199 patients with metastatic CRPC in a 2/1 fashion between enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not requested but possible, and therefore received by 30% of the population. The primary end-point was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, $P < 0.001$). This led to the recommendation that the study be halted and unblinded. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA or objective progression). No difference in terms of side effects were observed in the 2 groups, with a lower incidence of grade 3-4 side effects in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

20.11.3 ***Abiraterone acetate***

Abiraterone acetate is a CYP17 inhibitor. It is used once daily combined with prednisone twice daily (10 mg/day). Positive preliminary results of the large phase III COU-AA-301 trial were reported after a median follow-up of 12.8 months (110) and the final results have been reported more recently (111). A total of 1,195 patients with metastatic CRPC were randomised in a 1/1 fashion between abiraterone acetate or placebo. All patients had progressive disease based on the PCWG2 criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary end-point was OS, with a planned HR of 0.8 in favour of abiraterone. After a median follow-up of 20.2 months, the median survival in the abiraterone group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, $P < 0.001$). The benefit was observed irrespective of age, baseline pain intensity, and type of progression. All the secondary objectives were in favour of abiraterone

(PSA, radiologic tissue response, time to PSA or objective progression). With regard to previous docetaxel therapy, no benefit was observed in the abiraterone arm when docetaxel had been used for < 3 months, but the benefit remained independent of the delay since the last dose of docetaxel (less or more than 3 months). The incidence of the most common grade 3/4 side effects did not differ significantly between both arms, but mineralocorticoid-related side effects were more frequent in the abiraterone group, mainly grade 1/2 (fluid retention, oedema or hypokalaemia). The longer follow-up did not lead to an unexpected increased in toxicity compared to the preliminary analysis.

However, the choice between third-line hormonal treatment (using enzalutamide or abiraterone) or second-line chemotherapy (cabazitaxel) remains unclear with no clear decision-making findings published. They are urgently awaited because nothing is known regarding the optimal sequencing of drugs. The cost of each drug will be a major challenge to public health.

Recommendations on salvage treatment after Docetaxel	LE	GR
Cabazitaxel is a valid option for management of progressive CRPC following docetaxel therapy.	1b	A
Abiraterone and enzalutamide are both valid options for management of progressive CRPC following docetaxel therapy.	1b	A
No definitive strategy regarding treatment choice (which drug/which drug family first) can be devised	4	

CRPC = castration-resistant prostate cancer.

20.12 Palliative therapeutic options: bone targeted therapies in CRPC

CRPC is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is often required with input from medical oncologists, radiation oncologists, urologists, nurses, psychologists and social workers (112).

20.12.1 ***Painful bone metastases***

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective (113), even as single fraction (114). The two radioisotopes, strontium-89 and samarium-153, can partially or completely decrease bone pain in up to 70% of patients, but should not be given too late when pain is intractable. Early use can give rise to myelosuppression, making subsequent chemotherapy more difficult (115), even though a recent phase I trial has demonstrated manageable haematological toxicity with repeated administration of docetaxel and samarium-153. The use of samarium-153 as consolidation therapy, following a clear docetaxel response, may also help with initially painful bone metastases (116). Apart from the OS benefit, the α-radioisotope emitter, radium-233, has also shown a significant palliative effect in patients with painful bone metastases (117). The full results of this study are urgently awaited.

20.12.2 ***Common complications due to bone metastases***

Common complications due to bone metastases include bone pain, vertebral collapse or deformity, pathological fractures and spinal cord compression. Osteoporosis may also cause fractures and should be prevented (see above). Cementation is an effective treatment for painful fracture, clearly improving both pain and QoL (118). However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases (119,120). Impending spinal cord compression is an emergency. It must be recognised early and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery consultation should be planned to discuss a possible decompression (121). Otherwise, external beam radiotherapy, with or without systemic therapy, is the treatment of choice.

20.12.3 ***Bisphosphonates***

Bisphosphonates have been used to inhibit osteoclast-mediated bone resorption and osteoclast precursors in CRPC. In the largest single phase III trial to date (122), 643 patients who had CRPC with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every 3 weeks for 15 consecutive months, or placebo. At 15 and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer skeletal-related events (SREs) compared to the placebo group (44% vs. 33%, P = 0.021) and fewer pathological fractures (13.1% vs. 22.1%, P = 0.015). Furthermore, the time to first SRE was longer in the zoledronic acid group, thus improving QoL. Patients were initially randomised to 4 or 8 mg of zoledronic acid, but the 8 mg dosage was later modified to 4 mg because of toxicity. No survival benefit was seen in any trial with bisphosphonates, except in a post hoc analysis of an old compound without any significant impact on SREs (123).

Currently, bisphosphonates can be offered to patients with CRPC bone metastases to prevent skeletal complications, even if the best dosing interval is unclear. At present, it is every 3 weeks or less. The toxicity (e.g., jaw necrosis) of these drugs, especially aminobisphosphonate, must always be kept in mind (122). Patients should have a dental examination before starting bisphosphonate therapy. The risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection, as well as intravenous long-term bisphosphonate administration (124).

Pain due to bone metastases is one of the most debilitating complications of CRPC. Bisphosphonates have proven to be highly effective in reducing bone pain, but so far this has been investigated only in small, open trials. Data from these trials suggest that bisphosphonates have a low side-effect profile (125-127). Bisphosphonates should be considered early in the management of symptomatic CRPC. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which often occur (i.e., palliative external beam radiation, cortisone, analgesics and antiemetics).

20.12.4 ***RANK ligand inhibitors***

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κB ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-metastasis-free survival compared to placebo (median benefit: 4.2 months, HR: 0.85, P = 0.028) (128). However, this benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively). The practical impact of this finding remains under discussion. The efficacy and safety of denosumab (n = 950) compared with zoledronic acid (n = 951) in patients with metastatic CRPC was assessed in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs, as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 vs. 17.1 months, respectively (HR 0.82; P = 0.008). Denosumab also extended time to first and subsequent on-study SRE (HR 0.82; P = 0.008). Both urinary NTX and BAP were significantly suppressed in the denosumab arm compared with the zoledronic acid arm (P < 0.0001 for both). However, these positive findings were not associated with any survival benefit. Denosumab is FDA approved for preventing SREs in patients with bone metastases from solid tumours, and EMEA approval is pending.

20.13 Summary of treatment after hormonal therapy (first second-line modality)

Recommendations	GR
It is recommended to stop anti-androgen therapy once PSA progression is documented.	B
No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormonotherapy or chemotherapy) as no clear predictive factors exist.	C
Second-line salvage hormonal treatment using abiraterone acetate is considered to be a valid option. It must be remembered that one of the 2 coprimary end-points of the pivotal trial has not yet been met.	A
Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.	

PSA = prostate-specific antigen.

20.14 Cytotoxic and pre/post-docetaxel therapy in CRPC

Recommendations	GR
Patients with CRPC should be counselled, managed and treated by a multidisciplinary team.	
In non-metastatic CRPC, cytotoxic therapy should only be used in a clinical trial setting.	B
In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented.	B
Patients should not be started on second-line therapy unless their testosterone serum levels are < 50 ng/dL.	B
Patients should not be started on second-line therapy unless their PSA serum levels are > 2 ng/mL to ensure correct interpretation of therapeutic efficacy.	B
Prior to treatment, the potential benefits of second-line therapy and expected side effects should be discussed with the patient.	C
In patients with metastatic CRPC who are candidates for cytotoxic therapy, docetaxel at 75 mg/m^2 every 3 weeks is the drug of choice because it has shown a significant survival benefit.	A

If chemotherapy is considered in patients with symptomatic bone metastases due to CRPC, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable options. If not contraindicated, docetaxel is the preferred agent based on the significant advantage in pain relief.	A
In patients with relapse following first-line docetaxel chemotherapy cabazitaxel, abiraterone and enzalutamide are regarded as first-choice options for second-line treatment.	A
Second-line docetaxel can be offered to previously responding docetaxel-treated patients.	B
Otherwise, treatment should be tailored to the individual patient. In case patients are not eligible for cabazitaxel, abiraterone or enzalutamide, docetaxel re-challenge is an option.	A
In men with CRPC with symptomatic bone metastases, who are ineligible for or progressing after docetaxel treatment with 223Ra (alpharadin) has shown a survival benefit.	A

CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen.

20.15 Recommendations for "non-specific" management of CRPC

Recommendations	GR
Management of patients with extended symptomatic bone metastases has to be directed at improvement of QoL and mainly pain reduction.	A
Effective medical management with the highest efficacy and a low frequency of side-effects is the major goal of therapy.	A
Bone protective agents may be offered to patients with skeletal metastases (denosumab being superior to zoledronic acid) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.	A
Calcium and vitamine D supplementation must be systematically considered when using either Denosumab or biphosphonates.	A
In the management of painful bone metastases, early use of palliative treatments such as radionuclides, external beam radiotherapy and adequate use of analgesics is recommended.	B
In patients with neurological symptoms, spinal surgery or decompressive radiotherapy might be indicated as emergency interventions. High-dose corticosteroids must be always initially considered.	A

20.16 References

1. Chi KN, Bjartell A, Dearnaley D, et al. Castration-resistant prostate cancer: from new pathophysiology to new treatment targets. Eur Urol. 2009 Oct;56(4):594-605. http://www.ncbi.nlm.nih.gov/pubmed/19560857
2. Attard G, Cooper CS, de Bono JS. Steroid hormone receptors in prostate cancer: a hard habit to break? Cancer Cell 2009 Dec 8;16(6):458-62. http://www.ncbi.nlm.nih.gov/pubmed/19962664
3. Schröder FH. Progress in understanding androgen-independent prostate cancer (AIPC): a review of potential endocrine-mediated mechanisms. Eur Urol 2008 Jun;53(6):1129-37. http://www.ncbi.nlm.nih.gov/pubmed/18262723
4. Haldar S, Basu A, Croce CM. Bcl-2 is the guardian of microtubule integrity. Cancer Res 1997 Jan;57(2):229-33. http://www.ncbi.nlm.nih.gov/pubmed/9000560
5. Stapleton AM, Timme TL, Gousse AE, et al. Primary human prostate cancer cells harboring p53 mutations are clonally expanded in metastases. Clin Cancer Res 1997 Aug;3(8):1389-97. http://www.ncbi.nlm.nih.gov/pubmed/9815823
6. Theodorescu D, Broder SR, Boyd JC, et al. p53, bcl-2 and retinoblastoma proteins as long-term prognostic markers in localized carcinoma of the prostate. J Urol 1997 Jul;158(1):131-7. http://www.ncbi.nlm.nih.gov/pubmed/9186339
7. MacGrogan D, Bookstein R. Tumour suppressor genes in prostate cancer. Semin Cancer Biol 1997 Feb;8(1):11-9. http://www.ncbi.nlm.nih.gov/pubmed/9299577
8. Chi KN. Targeting Bcl-2 with oblimersen for patients with hormone refractory prostate cancer. World J Urol 2005 Feb;23(1):33-7. http://www.ncbi.nlm.nih.gov/pubmed/15723221
9. Zhang Z, Li M, Wang H, Agrawal S, et al. Antisense therapy targeting MDM2 oncogene in prostate cancer: Effects on proliferation, apoptosis, multiple gene expression, and chemotherapy. Proc Natl Acad Sci USA 2003 Sep;100(20):11636-41. http://www.ncbi.nlm.nih.gov/pubmed/13130078

10. Verhagen PC, van Duijn PW, Hermans KG, et al. The PTEN gene in locally progressive prostate cancer is preferentially inactivated by bi-allelic gene deletion. J Pathol 2006 Apr;208(5):699-707. http://www.ncbi.nlm.nih.gov/pubmed/16402365
11. Hu R, Dunn TA, Wei S, et al. Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone-refractory prostate cancer. Cancer Res 2009 Jan;69(1):16-22. http://www.ncbi.nlm.nih.gov/pubmed/19117982
12. Linja MJ, Savinainen KJ, Saramäki OR, et al. Amplification and overexpression of androgen receptor gene in hormone-refractory prostate cancer. Cancer Res. 2001 May 1;61(9):3550-5. http://www.ncbi.nlm.nih.gov/pubmed/11325816
13. Ruijter E, van de Kaa C, Miller G, et al. Molecular genetics and epidemiology of prostate carcinoma. Endocr Rev 1999 Feb;20(1):22-45. http://www.ncbi.nlm.nih.gov/pubmed/10047972
14. Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res 2008 Jun;68(11):4447-54. http://www.ncbi.nlm.nih.gov/pubmed/18519708
15. Locke JA, Guns ES, Lubik AA, et al. Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. Cancer Res 2008 Aug;68(15):6407-15. http://www.ncbi.nlm.nih.gov/pubmed/18676866
16. Stanbrough M, Bubley GJ, Ross K, et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. Cancer Res 2006 Mar;66(5):2815-25. http://www.ncbi.nlm.nih.gov/pubmed/16510604
17. Taplin ME, Rajeshkumar B, Halabi S, et al. Cancer and Leukemia Group B Study 9663. Androgen receptor mutations in androgen-independent prostate cancer: Cancer and Leukemia Group B Study 9663. Clin Oncol 2003 Jul;21(14):2673-8. http://www.ncbi.nlm.nih.gov/pubmed/12860943
18. Tomlins SA, Rhodes DR, Perner S, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 2005 Oct;310(5748):644-8. http://www.ncbi.nlm.nih.gov/pubmed/16254181
19. Scher HI, Halabi S, Tannock I, et al. Prostate Cancer Clinical Trials Working Group. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008 Mar;26(7):1148-59. http://www.ncbi.nlm.nih.gov/pubmed/18309951
20. Heidenreich A, von Knobloch R, Hofmann R. Current status of cytotoxic chemotherapy in hormone refractory prostate cancer. Eur Urol 2001 Feb;39(2):121-30. http://www.ncbi.nlm.nih.gov/pubmed/11223670
21. Yamaoka M, Hara T, Kusaka M. Overcoming Persistent Dependency on Androgen Signaling after Progression to Castration-Resistant Prostate Cancer. Clin Cancer Res September 1, 2010 16:4319-24. http://clincancerres.aacrjournals.org/content/16/17/4319
22. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009 Jan;45(2):228-47. http://www.ncbi.nlm.nih.gov/pubmed/19097774
23. Tombal B, Rezazadeh A, Therasse P, et al. Magnetic resonance imaging of the axial skeleton enables objective measurement of tumor response on prostate cancer bone metastases. Prostate 2005 Oct;65(2):178-87. http://www.ncbi.nlm.nih.gov/pubmed/15948151
24. Scher HI, Mazumdar M, Kelly WK. Clinical trials in relapsed prostate cancer: defining the target. J Natl Cancer Inst 1996 Nov;88(22):1623-34. http://www.ncbi.nlm.nih.gov/pubmed/8931606
25. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol 2006 Jul;24(19):3089-94. http://www.ncbi.nlm.nih.gov/pubmed/16809734
26. Kantoff P W, Schuetz T, Blumenstein BA, et al. Overall survival (OS) analysis of a phase II randomized controlled trial (RCT) of a poxviral-based PSA targeted immunotherapy in metastatic castration resistant prostate cancer (mCRPC). J Clin Oncol 27:15s, 2009 (suppl; abstract #5013) http://www.ncbi.nlm.nih.gov/pubmed/20100959

27. Bellmunt J, Rosenberg JE, Choueiri TK. Recent progress and pitfalls in testing novel agents in castration-resistant prostate cancer. Eur Urol 2009 Oct;56(4):606-8. http://www.ncbi.nlm.nih.gov/pubmed/19635642
28. Dawson NA, McLeod DG. The assessment of treatment outcomes in metastatic prostate cancer: changing endpoints. Eur J Cancer 1997 Apr;33(4):560-5. http://www.ncbi.nlm.nih.gov/pubmed/9274435
29. Kelly WK, Scher HI, Mazurmdar M, et al. Prostate-specific antigen as a measure of disease outcome in metastatic hormone-refractory prostate cancer. J Clin Oncol 1993 Apr;11(4):607-15. http://www.ncbi.nlm.nih.gov/pubmed/7683043
30. Sella A, Kilbourn R, Amato R, et al. Phase II study of ketoconazole combined with weekly doxorubicinin patients with androgen-independent prostate cancer. J Clin Oncol 1994 Apr;12(4):683-8. http://www.ncbi.nlm.nih.gov/pubmed/7512126
31. Pienta KJ, Redman B, Hussain M, et al. Phase II evaluation of oral estramustine and oral etoposide inhormone-refractory adenocarcinoma of the prostate. J Clin Oncol 1994 Oct;12(10):2005-12. http://www.ncbi.nlm.nih.gov/pubmed/7523606
32. Hudes GR, Greenberg R, Krigel RL, et al. Phase II study of estramustine and vinblastine, two microtubule inhibitors, in hormone-refractory prostate cancer. J Clin Oncol 1992 nov;10(11):1754-61. http://www.ncbi.nlm.nih.gov/pubmed/1383436
33. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative endpoints. J Clin Oncol 1996 Jun;14(6):1756-64. http://www.ncbi.nlm.nih.gov/pubmed/8656243
34. George DJ, Kantoff PW. Prognostic indicators in hormone refractory prostate cancer. Urol Clin NorthAm 1999 May;26(2):303-10. http://www.ncbi.nlm.nih.gov/pubmed/10361553
35. Scher HI, Curley T, Geller N, et al. Trimetrexate in prostatic cancer: preliminary observations on the use of prostate-specific antigen and acid phosphatase as a marker in measurable hormone-refractory disease. J Clin Oncol 1990 Nov;8(11):1830-8. http://www.ncbi.nlm.nih.gov/pubmed/1700078
36. Kelly WK, Scher HI, Mazurmdar M, et al. Prostate-specific antigen as a measure of disease outcomein metastatic hormone-refractory prostate cancer. J Clin Oncol 1993 Apr;11(4):607-15. http://www.ncbi.nlm.nih.gov/pubmed/7683043
37. Smith DC, Dunn RL, Strawderman MS, et al. Change in serum prostate-specific antigen as a marker of response to cytotoxic therapy for hormone-refractory prostate cancer. J Clin Oncol 1998 May;16(5):1835-43. http://www.ncbi.nlm.nih.gov/pubmed/9586898
38. Petrylak DP, Ankerst DP, Jiang CS, et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16.Crawford ED. J Natl Cancer Inst. 2006 Apr 19;98(8):516-21. http://www.ncbi.nlm.nih.gov/pubmed/16622120
39. Armstrong AJ, Garrett-Mayer E, de Wit R, et al. Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. Clin Cancer Res. 2010 Jan 1;16(1):203-11. http://www.ncbi.nlm.nih.gov/pubmed/20008841
40. Scher HI, Jia X, de Bono JS, et al. Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. Lancet Oncol 2009 Mar;10(3):233-9. http://www.ncbi.nlm.nih.gov/pubmed/19213602
41. Helo P, Cronin AM, Danila DC, et al. Circulating prostate tumor cells detected by reverse transcription-PCR in men with localized or castration-refractory prostate cancer: concordance with Cell Search assay and association with bone metastases and with survival. Clin Chem 2009 Apr;55(4):765-73. http://www.ncbi.nlm.nih.gov/pubmed/19233911
42. Goodman OB Jr, Fink LM, Symanowski JT, et al. Circulating tumor cells in patients with castrationresistant prostate cancer baseline values and correlation with prognostic factors. Cancer Epidemiol Biomarkers Prev 2009 Jun;18(6):1904-13. http://www.ncbi.nlm.nih.gov/pubmed/19505924
43. Heidenreich A, Hofmann R, Engelmann UH. The use of bisphosphonates for the palliative treatment of painful bone metastasis due to hormone refractory prostate cancer. J Urol 2001 Jan;165(1):136-40. http://www.ncbi.nlm.nih.gov/pubmed/11125382

44. Berthold DR, Pond GR, Roessner M et al. TAX-327 investigators. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. Clin Cancer Res 2008 May 1;14(9): 2763-7.
http://www.ncbi.nlm.nih.gov/pubmed/18451243
45. Klugo RC, Farah RN, Cerny JC. Bilateral orchiectomy for carcinoma of the prostate. Response of serum testosterone and clinical response to subsequent estrogen therapy. Urology 1981 Jan;17(1): 49-50.
http://www.ncbi.nlm.nih.gov/pubmed/7456197
46. Manni A, Bartholomew M, Caplan R, et al. Androgen priming and chemotherapy in advanced prostate cancer: evaluation of determinants of clinical outcome. J Clin Oncol 1988 Sep;6(9):1456-66.
http://www.ncbi.nlm.nih.gov/pubmed/3047336
47. Taylor CD, Elson P, Trump DL. Importance of continued testicular suppression in hormone-refractory prostate cancer. J Clin Oncol 1993 nov;11(11):2167-72.
http://www.ncbi.nlm.nih.gov/pubmed/8229130
48. Hussain M, Wolf M, Marshall E, et al. Effects of continued androgen deprivation therapy and other prognostic factors on response and survival in phase II chemotherapy trials for hormone-refractory prostate cancer: a Southwest Oncology Group report. J Clin Oncol 1994 Sep;12(9):1868-75.
http://www.ncbi.nlm.nih.gov/pubmed/8083710
49. Ryan CJ, Small EJ. Role of secondary hormonal therapy in the management of recurrent disease. Urology 2003 Dec;62(Suppl 1):87-94.
http://www.ncbi.nlm.nih.gov/pubmed/14747046
50. Scher HI, Kelly WK. Flutamide withdrawal syndrome: its impact on clinical trials in hormone-refractory prostate cancer. J Clin Oncol 1993 Aug;11(8):1566-72.
http://www.ncbi.nlm.nih.gov/pubmed/7687666
51. Small EJ, Carroll PR. Prostate-specific antigen decline after casodex withdrawal: evidence for an antiandrogen withdrawal syndrome. Urology 1994 Mar;43(3):408-10.
http://www.ncbi.nlm.nih.gov/pubmed/7510915
52. Dawson NA, McLeod DG. Dramatic prostate specific antigen decline in response to discontinuation of megestrol acetate in advanced prostate cancer: expansion of the antiandrogen withdrawal syndrome. J Urol 1995 Jun;153(6):1946-7.
http://www.ncbi.nlm.nih.gov/pubmed/7538601
53. Small EJ, Vogelzang NJ. Second-line hormonal therapy for advanced prostate cancer: a shifting paradigm. J Clin Oncol 1997 Jan;15(1):382-8.
http://www.ncbi.nlm.nih.gov/pubmed/8996165
54. Scher HI, Liebertz C, Kelly WK, et al. Bicalutamide for advanced prostate cancer: the natural versus treated history of disease. J Clin Oncol 1997 Aug;15(8):2928-38.
http://www.ncbi.nlm.nih.gov/pubmed/9256137
55. Joyce R, Fenton MA, Rode P, et al. High dose bicalutamide for androgen independent prostate cancer: effect of prior hormonal therapy. J Urol 1998 Jan;159(1):149-53.
http://www.ncbi.nlm.nih.gov/pubmed/9400459
56. Kucuk O, Blumenstein B, Moinpour C, et al. Phase II trial of Casodex in advanced prostate cancer (CaP) patients who failed conventional hormonal manipulations: a Southwest Oncology Group study(SWOG 9235). Proc Am Soc Clin Oncol (ASCO) 1996;15:245 (abstr).
57. Osborn JL, Smith DC, Trump DL. Megestrol acetate in the treatment of hormone refractory prostate cancer. Am J Clin Oncol 1997 Jun;20(3):308-10.
http://www.ncbi.nlm.nih.gov/pubmed/9167760
58. Gebbia V, Testa A, Gebbia N. Prospective randomized trial of two dose levels of megestrol acetate in the management of anorexia-cachexia syndrome in patients with metastatic cancer. Br J Cancer 1996Jun;73(12):1576-80.
http://www.ncbi.nlm.nih.gov/pubmed/8664133
59. Dawson NA, Conaway M, Halabi S, et al. A randomized study comparing standard versus moderately high dose megestrol acetate for patients with advanced prostate carcinoma: cancer and leukaemia group B study 9181. Cancer 2000 Feb;88(4):825-34.
http://www.ncbi.nlm.nih.gov/pubmed/10679652
60. Sartor AO, Tangen CM, Hussain MH, et al. Southwest Oncology Group. Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). Cancer 2008Jun;112(11):2393-400.
http://www.ncbi.nlm.nih.gov/pubmed/18383517

61. McLeod DG. Antiandrogenic drugs. Cancer 1993 Feb;71(3 Suppl):1046-9.
http://www.ncbi.nlm.nih.gov/pubmed/8428326
62. Kucuk O, Fisher E, Moinpour CM, et al. Phase II trial of bicalutamide in patients with advanced prostate cancer in whom conventional hormonal therapy failed: a Southwest Oncology Group study (SWOG 9235). Urology 2001 Jul;58(1):53-8.
http://www.ncbi.nlm.nih.gov/pubmed/11445479
63. Sartor O, Gomella LG, Gagnier P, et al. Dutasteride and bicalutamide in patients with hormonerefractory prostate cancer: the Therapy Assessed by Rising PSA (TARP) study rationale and design. Can J Urol 2009 Oct;16(5):4806-12.
http://www.ncbi.nlm.nih.gov/pubmed/19796455
64. Dawson NA. Treatment of progressive metastatic prostate cancer (published erratum of serious dosage error appears in Oncology (Huntingt) 1993 Jun;7(6):2). Oncology 1993 May;7(5):17-24, 27; discussion 27-9.
http://www.ncbi.nlm.nih.gov/pubmed/8512779
65. Fowler JE Jr, Pandey P, Seaver LE, et al. Prostate specific antigen after gonadal androgen withdrawal deferred flutamide treatment. J Urol 1995 Aug;154(2 Pt 1):448-53.
http://www.ncbi.nlm.nih.gov/pubmed/7541862
66. Suzuki H, Okihara K, Miyake H, et al. Nonsteroidal Antiandrogen Sequential Alternation for Prostate Cancer Study Group. Alternative nonsteroidal antiandrogen therapy for advanced prostate cancer that relapsed after initial maximum androgen blockade. J Urol 2008 Sep;180(3):921-7.
http://www.ncbi.nlm.nih.gov/pubmed/18635218
67. Sartor O, Cooper M, Weinberger M, et al. Surprising activity of flutamide withdrawal, when combined with aminoglutethimide, in treatment of 'hormone refractory' prostate cancer. J Natl Cancer Inst 1994Feb;86(3):222-7.
http://www.ncbi.nlm.nih.gov/pubmed/7506794
68. Dupont A, Gomez JL, Cusan L, et al. Response to flutamide withdrawal in advanced prostate cancer in progression under combination therapy. J Urol 1993 Sep;150(3):908-13.
http://www.ncbi.nlm.nih.gov/pubmed/7688437
69. Rochlitz CF, Damon LE, Russi MB, et al. Cytotoxicity of ketoconazole in malignant cell lines. Cancer Chemother Pharmacol 1988;21(4):319-22.
http://www.ncbi.nlm.nih.gov/pubmed/3370740
70. Mahler C, Verhelst J, Denis L. Ketoconazole and liarozole in the treatment of advanced prostatic cancer. Cancer 1993 Feb;71(3 Suppl):1068-73.
http://www.ncbi.nlm.nih.gov/pubmed/8428329
71. Small EJ, Halabi S, Dawson NA, et al. Antiandrogen withdrawal alone or in combination with ketokonazole in androgen independent prostate cancer patients: a phase III trial (CALGB 9583). J ClinOncol 2004 Mar;22(6):1025-33.
http://www.ncbi.nlm.nih.gov/pubmed/15020604
72. Smith DC, Redman BG, Flaherty LE, et al. A phase II trial of oral diethylbestrol as a second line hormonal agent in advanced prostate cancer. Urology 1998 Aug;52(2):257-60.
http://www.ncbi.nlm.nih.gov/pubmed/9697791
73. Klotz L, McNeill I, Fleshner N. A phase 1-2 trial of diethylbestrol plus low dose warfarin in advanced prostate carcinoma. J Urol 1999 Jan;161(1):169-72.
http://www.ncbi.nlm.nih.gov/pubmed/10037391
74. Oh WK, Kanthoff PW, Weinberg V, et al. Prospective, multicentre, randomized phase II trial of the herbal supplement PC-SPES and diethylbestrol in patients with androgen-independent prostate cancer. Clin Oncol 2004 Sep;22(18):3705-12.
http://www.ncbi.nlm.nih.gov/pubmed/15289492
75. Ryan CJ, Smith MR, de Bono JS, et al. COU-AA-302 Investigators.Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013 Jan 10;368(2):138-48.
http://www.ncbi.nlm.nih.gov/pubmed/23228172
76. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantroneand prednisone for advanced refractory prostate cancer. New Engl J Med 2004 Oct;351(15):1513-20.
http://www.ncbi.nlm.nih.gov/pubmed/15470214
77. Tannock IF, de Wit R, Berry WR, et al. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. New Engl J Med 2004 Oct;351(15): 1502-12.
http://www.ncbi.nlm.nih.gov/pubmed/15470213

78. Eisenberger M, Garrett-Mayer ES, Ou Yang Y, et al. Multivariate prognostic nomogram incorporating PSA kinetics in hormone-refractory metastatic prostate cancer (HRPC). Abstract. ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2007;25(18S): #5058. http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/5058
79. Graff J, Lalani AS, Lee S, et al. ASCENT Investigators. C-reactive protein as a prognostic marker formen with androgen-independent prostate cancer (AIPC): Results from the ASCENT trial. Abstract. ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2007;25(18S):abstract #5074. http://www.ncbi.nlm.nih.gov/pubmed/18428198
80. Prins R, Rademacher BL, Mongoue-Tchokote S, et al. C-reactive protein as adverse prognostic marker for men with castration-resistant prostate cancer (CRPC): Confirmatory results. J Clin Oncol 27:15s,2009 (suppl; abstract #5168) http://www.ncbi.nlm.nih.gov/pubmed
81. Bompas E, Italiano A, Ortholan C, et al. Docetaxel-based chemotherapy in elderly patients (> 75 years) with castration resistant prostate cancer (CRPC): A French National study of 175 patients. Abstract. ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2008;26(15S): #5145. http://www.ncbi.nlm.nih.gov/pubmed/18706755
82. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the Cancer and Leukemia Group B 9182 Study. J Clin Oncol 1999 Aug;17(8):2506-13. http://www.ncbi.nlm.nih.gov/pubmed/10561316
83. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996 Jun;14(6):1756-64. http://www.ncbi.nlm.nih.gov/pubmed/8656243
84. Albrecht W, Van Poppel H, Horenblas S, et al. Randomized Phase II trial assessing estramustine and vinblastine combination chemotherapy vs estramustine alone in patients with progressive hormone-escaped metastatic prostate cancer. Br J Cancer. 2004 Jan 12;90(1):100-5. http://www.ncbi.nlm.nih.gov/pubmed/14710214
85. Fizazi K, Le Maitre A, Hudes G, et al. Meta-analysis of Estramustine in Prostate Cancer (MECaP) Trialists' Collaborative Group. Addition of estramustine to chemotherapy and survival of patients with castration-refractory prostate cancer: a meta-analysis of individual patient data. Lancet Oncol 2007Nov;8(11):994-1000. http://www.ncbi.nlm.nih.gov/pubmed/17942366
86. Lubiniecki GM, Berlin JA, Weinstein RB, et al. Risk of thromboembolic events (TE) with estramustine-based chemotherapy in hormone-refractory prostate cancer (HRPC): results of a meta-analysis. Abstract. Proc Am Soc Clin Oncol 2003;22: #1581. http://www.ncbi.nlm.nih.gov/pubmed/15536625
87. Maulard-Durdux C, Dufour B, Hennequin C, et al. Phase II study of the oral cyclophosphamide and oral etoposide combination in hormone-refractory prostate carcinoma patients. Cancer 1996 Mar;77(6):1144-8. http://www.ncbi.nlm.nih.gov/pubmed/8635136
88. Nelius T, Klatte T, de Riese W, et al. Clinical outcome of patients with docetaxel-resistant hormone-refractory prostate cancer treated with second-line cyclophosphamide-based metronomic chemotherapy. Med Oncol 2010 Jun;27(2):363-7. http://www.ncbi.nlm.nih.gov/pubmed/19365737
89. Smith DC, Chay CH, Dunn RL, et al. Phase II trial of paclitaxel, estramustine, etoposide and carboplatin in the treatment of patients with hormone-refractory prostate cancer. Cancer 2003 Jul;98(2):269-76. http://www.ncbi.nlm.nih.gov/pubmed/12872344
90. Regan MM, O'Donnell EK, Kelly WK, et al.Efficacy of carboplatin-taxane combinations in the management of castration-resistant prostate cancer: a pooled analysis of seven prospective clinical trials. Ann Oncol 2010 Feb;21(2):312-8. http://www.ncbi.nlm.nih.gov/pubmed/19633053
91. Heidenreich A, Sommer F, Ohlmann CH, et al. Prospective randomized phase II trial of pegylated doxorubicin in the management of symptomatic hormone refractory prostate carcinoma. Cancer 2004Sep;101(5):948-56. http://www.ncbi.nlm.nih.gov/pubmed/15329902

92. Savarese DM, Halabi S, Hars V, et al. Phase II study of docetaxel, estramustine, and low-dose hydrocortisone in men with hormone refractory prostate cancer: a final report of CALGB 9780. Cancer and Leukemia Group B. J Clin Oncol 2001 May;19(9):2509-16. http://www.ncbi.nlm.nih.gov/pubmed/11331330
93. Oudard S, Caty A, Humblet Y, et al. Phase II study of vinorelbine in patients with androgenindependent prostate cancer. Ann Oncol 2001 Jun;12(6):847-52. http://www.ncbi.nlm.nih.gov/pubmed/11484963
94. Carducci MA, Saad F, Abrahamsson PA, et al. Atrasentan Phase III Study Group Institutions. A phase3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormonerefractory prostate cancer. Cancer 2007 Nov;110(9):1959-66. http://www.ncbi.nlm.nih.gov/pubmed/17886253
95. Nelson JB, Fizazi K, Miller K, et al. Phase III study of the efficacy and safety of zibotentan (ZD4054) in patients with bone metastatic castration-resistant prostate cancer (CRPC). J Clin Oncol 2011; 29:suppl 7; abstr 117
96. Brady D, Parker CC, O'Sullivan JM. Bone-targeting radiopharmaceuticals including radium-223. Cancer J 2013 Jan;19(1):71-8. http://www.ncbi.nlm.nih.gov/pubmed/23337760
97. Bellmunt J. Tackling the bone with alpha emitters in metastatic castration-resistant prostate cancer patients. Eur Urol 2013 Feb;63(2):198-200. http://www.ncbi.nlm.nih.gov/pubmed/23062225
98. Kantoff PW, Higano CS, Shore ND, et al. IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010 Jul 29;363(5):411-22 http://www.ncbi.nlm.nih.gov/pubmed/20818862
99. Fosså SD, Jacobsen AB, Ginman C, et al. Weekly docetaxel and prednisolone versus prednisolone alone in androgen-independent prostate cancer: a randomized phase II study. Eur Urol 2007 Dec;52(6):1691-8. http://www.ncbi.nlm.nih.gov/pubmed/17306441
100. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010 Oct 2;376(9747):1147-54. http://www.ncbi.nlm.nih.gov/pubmed/20888992
101. Beer TM, Garzotto M, Henner WD, et al. Multiple cycles of intermittent chemotherapy in metastatic androgen-independent prostate cancer. Br J Cancer 2004;91(8):1425-7. http://www.ncbi.nlm.nih.gov/pubmed/15467765
102. Ohlmann C, Ozgur E, Wille S, et al. Second-line chemotherapy with docetaxel for prostate-specific antigen relapse in men with hormone refractory prostate cancer previously treated with docetaxel based chemotherapy. Eur Urol Suppl 2006;5(2):93, abstract #289.
103. Lara PN Jr, Twardowski P, Quinn DI. Angiogenesis-targeted therapies in prostate cancer. Clin Prostate Cancer 2004 Dec;3(3):165-73. http://www.ncbi.nlm.nih.gov/pubmed/15636683
104. Sternberg CN, Petrylak DP, Sartor O, et al. Multinational, double-blind, phase III study of Prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. J Clin Oncol 2009 Nov 10;27(32):5431-8 http://www.ncbi.nlm.nih.gov/pubmed/19805692
105. Ohlmann C, Ozgur E, Engelmann U, et al. Molecular triggered therapy in hormone refractory prostate cancer. Eur Urol Suppl 2006;5(2):93, abstract #281.
106. Ansari J, Hussain SA, Zarkar A, et al. Docetaxel re-treatment for metastatic hormone refractory prostate cancer. J Clin Oncol 2008;26(15S):abstract #16016. http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/16066
107. Periman PO, Sonpavde G, Bernold DM, et al. Sunitinib malate for metastatic castration resistant prostate cancer following docetaxel-based chemotherapy. J Clin Oncol 2008;26(15S):abstract #5157. http://www.ncbi.nlm.nih.gov/pubmed/19633050
108. Small EJ, Schellhammer PF, Higano CS, et al. Results of a placebo-controlled phase III trial of immunotherapy with APC8015 for patients with hormone refractory prostate Cancer (HRPC). J Clin Oncol 2005;23(16S):abstract #4500. http://www.ncbi.nlm.nih.gov/pubmed/16809734
109. Scher HI, Fizazi K, Saad F, et al. AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep 27;367(13):1187-97 http://www.ncbi.nlm.nih.gov/pubmed/22894553

110. de Bono JS, Logothetis CJ, Molina A, et al. COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011 May 26;364(21):1995-2005. http://www.ncbi.nlm.nih.gov/pubmed/21612468
111. Fizazi K, Scher HI, Molina A, et al. COU-AA-301 Investigators. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012 Oct;13(10):983-92. http://www.ncbi.nlm.nih.gov/pubmed/22995653
112. Esper PS, Pienta KJ. Supportive care in the patient with hormone refractory prostate cancer. Semin Urol Oncol 1997 Feb;15(1):56-64. http://www.ncbi.nlm.nih.gov/pubmed/9050140
113. Dy SM, Asch SM, Naeim A, et al. Evidence-based standards for cancer pain management. J Clin Oncol 2008 Aug;26(23):3879-85. http://www.ncbi.nlm.nih.gov/pubmed/18688056
114. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 2005 Jun;97(11):798-804. http://www.ncbi.nlm.nih.gov/pubmed/15928300
115. Liepe K, Kotzerke J. A comparative study of 188Re-HEDP, 186Re-HEDP, 153Sm-EDTMP and 89Sr in the treatment of painful skeletal metastases. Nucl Med Commun 2007 Aug;28(8):623-30. http://www.ncbi.nlm.nih.gov/pubmed/17625384
116. Morris MJ, Pandit-Taskar N, Stephenson RD, et al. Phase I study of docetaxel (Tax) and 153Sm repetitively administered for castrate metastatic prostate cancer (CMPC).). Abstract. J Clin Oncol May2008;26(15S): #5001. http://www.ncbi.nlm.nih.gov/pubmed/19364960
117. Parker C, Nilsson S, Heinrich D, et al. Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA). J Clin Oncol 2012; 30 (suppl ; abstr LBA4512). http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=95649
118. Frankel BM, Monroe T, Wang C. Percutaneous vertebral augmentation: an elevation in adjacent-level fracture risk in kyphoplasty as compared with vertebroplasty. Spine J. 2007 Sep-Oct;7(5):575-82.
119. Dutka J, Sosin P. Time of survival and quality of life of the patients operatively treated due to pathological fractures due to bone metastases. Ortop Traumatol Rehabil 2003 Jun;5(3):276-83. http://www.ncbi.nlm.nih.gov/pubmed/18034018
120. Frankel BM, Jones T, Wang C. Segmental polymethyl methacrylate-augmented pedicle screw Fixation in patients with bone softening caused by osteoporosis and metastatic tumor volvement: a clinical evaluation. Neurosurgery 2007 Sep;61(3):531-7; discussion 537-8. http://www.ncbi.nlm.nih.gov/pubmed/17881965
121. Marco RA, Sheth DS, Boland PJ, et al. Functional and oncological outcome of acetabular reconstruction for the treatment of metastatic disease. J Bone Joint Surg Am 2000 May;82(5):642-51. http://www.ncbi.nlm.nih.gov/pubmed/10819275
122. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002 Oct;94(19):1458-68. http://www.ncbi.nlm.nih.gov/pubmed/12359855
123. Dearnaley DP, Mason MD, Parmar MK, et al. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. Lancet Oncol. 2009 Sep;10(9):872-6 http://www.ncbi.nlm.nih.gov/pubmed/19674936
124. Aapro M, Abrahamsson PA, Body JJ, et al. Guidance on the use of bisphosphonates in solid tumours:recommendations of an international expert panel. Ann Oncol 2008 Mar;19(3):420-32. http://www.ncbi.nlm.nih.gov/pubmed/17906299
125. Diel IJ, Fogelman I, Al-Nawas B, et al. Pathophysiology, risk factors and management of bisphosphonate-associated osteonecrosis of the jaw: Is there a diverse relationship of amino- and non-aminobisphosphonates? Crit Rev Oncol Hematol 2007 Dec;64(3):198-207. http://www.ncbi.nlm.nih.gov/pubmed/17855108
126. Heidenreich A, Hofmann R, Engelmann. UH The use of bisphosphonate for the palliative treatment of painful bone metastasis due to hormone refractory prostate cancer. J Urol 2001 Jan;165(1):136-40. http://www.ncbi.nlm.nih.gov/pubmed/11125382

127. Heidenreich A, Elert A, Hofmann R. Ibandronate in the treatment of prostate cancer associated painful osseous metastases. Prostate Cancer Prostatic Dis 2002;5(3):231-5.
http://www.ncbi.nlm.nih.gov/pubmed/12496987
128. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet. 2012 Jan 7;379(9810):39-46
http://www.ncbi.nlm.nih.gov/pubmed/22093187

21. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

3D-US	three-dimensional ultrasound
ADT	androgen-deprivation therapy
AR	androgen-receptor
AS	active surveillance
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Therapeutic Radiology and Oncology
AUA	American Urological Association
BCF	biochemical failure
BCR	biochemical recurrence
BDFS	biochemical disease-free survival
BMD	bone mineral density
bNED	actuarial biochemical freedom from disease
CAB	complete (or maximal or total) androgen blockade
CAD	complete androgen deprivation
CPA	cyproterone acetate
CRT	conformal radiotherapy
CRPC	castration-resistant prostate cancer
CSAP	cryosurgical ablation of the prostate
CSS	cancer-specific survival
CT	computed tomography
CTC	circulating tumour cells
DES	diethylstilboestrol
DRE	digital rectal anticipation
DHT	dihydrostestosterone
DSS	disease-specific survival
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EGF	epidermal growth factor
eLND	extended lymph node dissection
ELND	elective lymph node dissection
EMA	European Medicines Agency
e-MRI	endorectal MRI
EORTC	European Organisation for Research and Treatment of Cancer
EPC	Early Prostate Cancer Trialists' Group
EPCP	Early Prostate Cancer Programme
EPE	extraprostatic extension
ER-®	oestrogen receptor-®
ESRPC	European Randomized Screening for Prostate Cancer
FACT-P	Functional Assessment of Cancer Therapy-prostate
FDA	Food and Drug Administration
FNAB	fine-needle aspiration biopsy
FSH	follicle-stimulating hormone
GI	gastrointestinal
GR	grade of recommendation
GU	genitourinary
HD EBRT	high-dose EBRT
HDR	high-dose rate
HIFU	high-intensity focused ultrasound
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
HRQoL	health-related quality of life
HT	hormonal therapy
IAD	intermittent androgen deprivation
IGRT	image-guided radiotherapy
IMRT	intensity modulated radiotherapy
IPSS	International Prostatic Symptom Score
LDAT	long-term ADT

LDR	low-dose rate (LDR)
LE	level of evidence
LET	linear energy transfer
LH	luteinising hormone
LHRH	luteinising hormone-releasing hormone
LHRHa	luteinising hormone-releasing hormone analogue
LND	lymph node dissection
LRP	laparoscopic radical prostatectomy
MRC	Medical Research Council
MRI	magnetic resonance imaging
MRSI	magnetic resonance spectroscopy imaging
NHT	neoadjvant hormonal therapy
NIH	National Institutes of Health
NVB	neurovascular bundle
OR	odds ratio
OS	overall survival
PAP	prostate acid phosphatase
PCa	prostate cancer
PET	positron emission tomography
PFS	progression-free survival
PIN	prostatic intraepithelial neoplasia
PIVOT	Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative StudiesProgram #407
PLCO	Prostate, Lung, Colorectal and Ovary
PSA	prostate-specific antigen
PSA-ACT	PSA complexed to antichymotrypsin
PSADT	PSA doubling time
PSAV	PSA velocity
PSMA	prostate-specific membrane antigen for messenger RNA
QoL	quality of life
QUALYs	quality of life adjusted gain in life
RALP	robot-assisted radical prostatectomy
RECIST	Response Evaluation Criteria In Solid Tumours
RITA	radio-frequency interstitial tumour ablation
RP	radical prostatectomy
RRP	radical retropubic prostatectomy
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
SCAP	salvage cryoablation of the prostate
SEER	Surveillance, Epidemiology, and End Results
SLN	sentinel lymph node
SLRP	salvage laparoscopic radical prostatectomy
SPCG-4	Scandinavian Prostate Cancer Group Study Number 4
SRE	skeletal-related events
SRP	salvage radical prostatectomy
SRT	salvage radiotherapy
STAD	short-term androgen deprivation
SVI	seminal vesicle invasion
SWOG	South West Oncology Group
TNM	Tumour Node Metastasis
TZ	transition zone
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate
UI	urinary incontinence
UICC	Union Against Cancer
USPIO	ultra-small super-paramagnetic iron oxide particles
VACURG	Veterans Administration Co-operative Urological Research Group
WHO	World Health Organization
WW	watchful waiting

Conflict of interest

All members of the Prostate Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.