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Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

NATIONAL PRACTICE GUIDELINE ON THE TREATMENT OF LOCALISED PROSTATE CANCER – PART 2

KCE REPORT 226
GOOD CLINICAL PRACTICE

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NATIONAL PRACTICE GUIDELINE ON THE TREATMENT OF LOCALISED PROSTATE CANCER – PART 2

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
3DCRT	three-dimensional conformal radiation therapy
A	Ablatherm
ADT	Androgen deprivation therapy
AE	adverse event
AGREE	Appraisal of guidelines for research and evaluation
AHRQ	Agency for Healthcare Research and Quality
AS	Active surveillance
ASA	American Society of Anaesthesiology
ASAP	Atypical glands suspicious for cancer
ASTRO definition	Three successive PSA increases above the nadir
AUA	American Urological Association
BCR	biochemical recurrence
BDFS	Biochemical disease free survival
BOO	bladder outlet obstruction
CDSR	Cochrane Database of Systematic Review
CPG	Clinical practice guideline
DRE	Digital rectal examination
EAU	European Association of Urology
EBRT	External beam radiation therapy
EPIC	Expanded Prostate Cancer Index Composite
ESUR	European Society of Urogenital Radiology
FACT-P	Functional Assessment of Cancer Therapy-Prostate
GDG	Guideline development group
GIN	Guidelines International Network
GL	Guideline
CG58	NICE's 2008 Prostate Cancer Guideline
CG175	NICE's 2014 Prostate Cancer Guideline
HGPIN	High-grade prostatic intraepithelial neoplasia
HIFU	High-intensity focused ultrasound

Horwitz definition	Two consecutive increases of at least 0.5 ng/ml
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
IGRT	Image-guided radiation therapy
IIEF-15	International Index of Erectile Function-15
IMRT	Intensity-modulated radiation therapy
INAMI – RIZIV	Institut national d'assurance maladie-invalidité – Rijksinstituut voor ziekte- en invaliditeitsverzekering
I-PSS	International Prostate Symptom Score
IQR	interquartile range
ISUP	International Society of Urological Pathology
KCE	Federaal Kenniscentrum voor de Gezondheidszorg – Centre Fédéral d'Expertise des Soins de Santé
LRP	Laparoscopic radical prostatectomy
MA	Meta-analysis
MeSH	Medical Subject Headings
MFSR	metastasis free survival rate
mo	month(s)
mpMRI	Multi-parametric Magnetic resonance Imaging
MRI	Magnetic resonance Imaging
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NNT	Number needed to treat
OMAR	Office of Medical Applications of Research
OS	overall survival rate
PCOS	Prostate Cancer Outcomes Study
PCSSR	prostate cancer specific survival rate
Phoenix definition	Biochemical failure as PSA nadir + 2 ng/ml
PICO	Participants–Interventions–Comparator–Outcomes
PIVOT	Prostate Cancer Intervention versus Observation Trial

PSA	Prostate specific antigen
QoL	Quality of Life
RARP	Robot assisted radical prostatectomy
RCT	Randomised controlled trial
RP	Radical prostatectomy
RR	Relative risk
RRP	Radical retropubic prostatectomy
RT	Radiotherapy
S	Sonoblate
SPC	suprapubic catheter
SPCG4	Scandinavian Prostate Cancer Group Study 4
SR	Systematic review
Stuttgart definition	Biochemical failure as PSA nadir +1.2 ng/ml
TPM	template prostate mapping
TRUS	Transrectal Ultrasonography
TURP	Transurethral resection of prostate
US	United States
UTI	urinary tract infection
VACURG	Veterans Administration Cooperative Urological Research Group
WW	Watchful waiting
yr	year

SCIENTIFIC REPORT

1. INTRODUCTION

1.1. Background

This report represents the second part of a Belgian national guideline on the treatment of localised prostate cancer. It is produced by experts assigned by the "College voor Oncologie – Collège de médecins d'Oncologie" in collaboration with the Belgian Health Care Knowledge Centre (KCE). In part-1 the role of watchful waiting/active surveillance was considered.[1] In a separate report, the KCE performed a qualitative study to discover factors that affect a patient's acceptance of active surveillance and a physician's willingness to offer active surveillance.[2]

The present guideline is related to the active treatment options (as opposed to active surveillance) of localised prostate cancer.

1.2. The need for a guideline

The development of clinical care pathways is one of the main actions described in the Belgian National Cancer Plan 2008-2010 and one of the assignments of the College of Oncology. For many years the Belgian Health Care Knowledge Centre (KCE) has collaborated with the College of Oncology. More precisely, it has provided scientific support in the development of clinical practice guidelines. So far, this collaboration has resulted in the publication of clinical practice guidelines on breast cancer, colorectal cancer, testicular cancer, pancreatic cancer, upper gastrointestinal cancer, cervical cancer, prostate cancer and lung cancer.

Besides the College of Oncology, two urologists in 2010 independently submitted to the KCE a "Topic Proposal" related to prostate cancer: one about high frequency ultrasound therapy and one on hormone therapy.

1.3. Overall objectives

This guideline provides recommendations based on current scientific evidence for the treatment of localised prostate cancer. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences.

1.4. Target users of the guideline

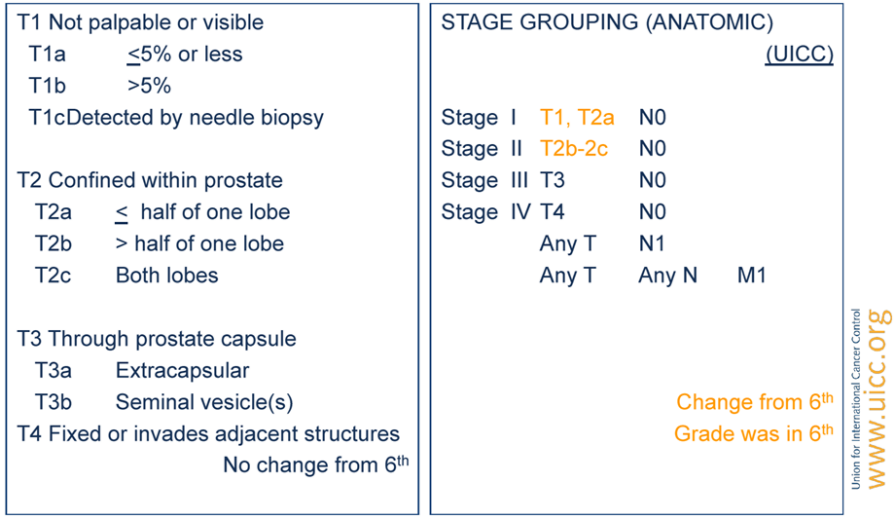
This guideline is intended to be used by care providers involved in the management of patients with localised prostate cancer, especially oncologists, urologists, and radiotherapists. It is also of interest to patients and their families, general practitioners, radiologists, and pathologists, nurses, hospital managers and policy makers.

1.5. Scope

1.5.1. TNM classification of prostate cancer

Staging of prostate cancer is accomplished through the TNM classification. It describes the extent of the primary tumour (T stage), the absence or presence of spread to nearby lymph nodes (N stage) and the absence or presence of metastasis (M stage). Figure 1 below describes the TNM classification from the Union for International Cancer Control (UICC - www.uicc.org). It represents the 7th edition (TNM-7) of the TNM classification that took effect in January 2010. The TNM system is used to describe the anatomical extent of disease. Different categories are further condensed into stage groups as shown in Figure 1.

Figure 1 – TNM classification of prostate cancer.



1.5.2. Risk stratification of prostate cancer

TNM staging is not suitable for prostate cancer treatment decisions since Gleason score and PSA (Prostate Specific Antigen) are far more important predictors of outcome, at least in the earlier stage of the disease.

The Gleason score is a pathologic concept related to the degree of differentiation of prostate cancer tissue. There is ongoing research in the development of the Gleason score. The present document refers to the 2011 definition.

PSA is a glycoprotein produced by cells of the prostate gland. The blood level of PSA is used as a tumour marker for men who may be suspected of having prostate cancer. Most physicians consider 0 to 4.0 ng/mL as the normal range. PSA levels have to be complemented with other tests to make a firm diagnosis of prostate cancer.[3]

Localised prostate cancer is classified into 3 categories according to the risk of progression by the European Association of Urology (EAU)[4]:

1. Low risk: T1-2a AND Gleason <7 AND PSA <10 ng/ml.
2. Intermediate risk: T2b-c OR Gleason 7 OR PSA 10-20 ng/ml.
3. High risk: T3a OR Gleason >7 OR PSA >20 ng/ml.

1.5.3. Scope of the present guideline

Clinicians generally understand the concept of localised prostate cancer as the clinical condition where the cancer is confined to the prostate gland in the absence of lymph node invasion or metastases (T1-T2 N0 M0). Some authors still consider T3a tumours as localised, while others would label them as locally advanced disease. In the present guideline the focus is on T1-T2 tumours.

As a result of an extensive deliberation with stakeholders in 2011, which included a web survey as described in part-1 of the national prostate cancer guideline,[1] it was decided not to consider issues related to diagnosis, follow-up, or the management of relapse after radical treatment. Furthermore, it was decided to conduct no formal cost-effectiveness assessments.

Part-1 of the Belgian national guideline considered the role of Watchful Waiting and Active Surveillance in patients with localised prostate cancer. It strongly recommended that in men with low-risk localised prostate cancer (1) active surveillance should be considered as a management option and (2) these patients must be informed that at the present time there is no demonstrated benefit within 10 to 12 years for immediate treatments as opposed to observation. For patients with intermediate risk cancer no general recommendation could be made on active surveillance. In patients with high-risk localised prostate cancer, active surveillance was not recommended.

The following clinical questions were defined:

- What is the role of surgery in the management of localised prostate cancer? What is the comparative effectiveness of different modes of surgery (open surgery, standard laparoscopic surgery, robot-assisted laparoscopic surgery) in terms of efficacy and side effects?
- What is the role of radiotherapy in the management of localised prostate cancer? What is the comparative effectiveness of different modes of radiotherapy (external radiotherapy, brachytherapy) in terms of efficacy and side effects?
- What is the role of HIFU (High Intensity Focused Ultrasound) in the management of localised prostate cancer?
- What is the place of hormonal therapy in the management of localised prostate cancer? Is there a role for hormones in mono-therapy? Is there a role for hormonal therapy as an adjuvant to surgery? Is there a role for hormonal therapy as an adjuvant to radiotherapy?

The clinical questions on HIFU and on hormones in mono-therapy were considered by the GDG of particular importance.

1.6. Statement of intent

Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of patients with localised prostate cancer.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all the available clinical data for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline are fully documented in the patient's file at the time the relevant decision is taken.

1.7. Funding and declaration of interest

KCE is a federal institution funded for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, Food chain Safety and Environment, and the Federal Public Service of Social Security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of guidelines is paid by KCE's budget, the sole mission of the KCE is providing scientifically valid information. KCE has no interest in companies (commercial or non-commercial i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of these guidelines. All clinicians involved in the Guideline Development Group (GDG) or the peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE researchers make yearly declarations of interest and further details of these are available upon request.

2. RECOMMENDATIONS

2.1. Patient information

Recommendation	Level of evidence	Strength of recommendation
• Prior to prostate cancer treatment, inform men and, if they wish, their partner that any active treatment may result in an alteration of sexual experience and may result in loss of sexual function.	NA	Strong
• Inform men and, if they wish, their partner about the potential loss of ejaculation and fertility associated with active treatment for prostate cancer. Discuss the possibility of sperm storage.	NA	Weak
• Inform men and if they wish, their partner of the potential effects on urinary function, particularly the risk of incontinence, and digestive function associated with active treatment for prostate cancer.	NA	Strong
• Offer a urological assessment to men who experience urinary symptoms before treatment of their prostate cancer.	NA	Strong
• Discuss the socio-economic impact of radical treatment, including potential professional disability and out-of pocket expenses, related to the management of adverse treatment effects.	NA	Strong

2.2. Radical treatment

Recommendation	Level of evidence	Strength of recommendation
• In men with localised prostate cancer to whom active surveillance has been proposed, but who decline, consider standard radical treatment with curative intent (i.e. radical prostatectomy, external beam radiotherapy or brachytherapy).	NA	Weak
• In men with intermediate risk localised prostate cancer, consider standard radical treatment with curative intent (i.e. radical prostatectomy, external beam radiotherapy or brachytherapy).	NA	Weak
• In men with high risk localised prostate cancer, offer standard radical treatment with curative intent (i.e. radical prostatectomy or external beam radiotherapy).	NA	Strong
• Do not offer adjuvant hormonal therapy in addition to radical prostatectomy to men with pN0, even to those with margin-positive disease.	NA	Strong
• In men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage.	NA	Strong
• In men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer a minimum dose equivalent to 74 Gy, delivered over 7-8 weeks to the prostate.	NA	Strong

• Do not offer brachytherapy as a unique radiotherapy modality to men with high-risk localised prostate cancer.	NA	Strong
• In men with intermediate risk localised prostate cancer treated with radical external beam radiotherapy, consider concomitant androgen deprivation therapy (ADT). Consider to give ADT for 6 months.	Low	Weak
• In men with high risk localised prostate cancer treated with radical external beam radiotherapy, offer concomitant androgen deprivation therapy (ADT). ADT should be continued beyond 6 months and for a maximum of 3 years.	Low	Strong

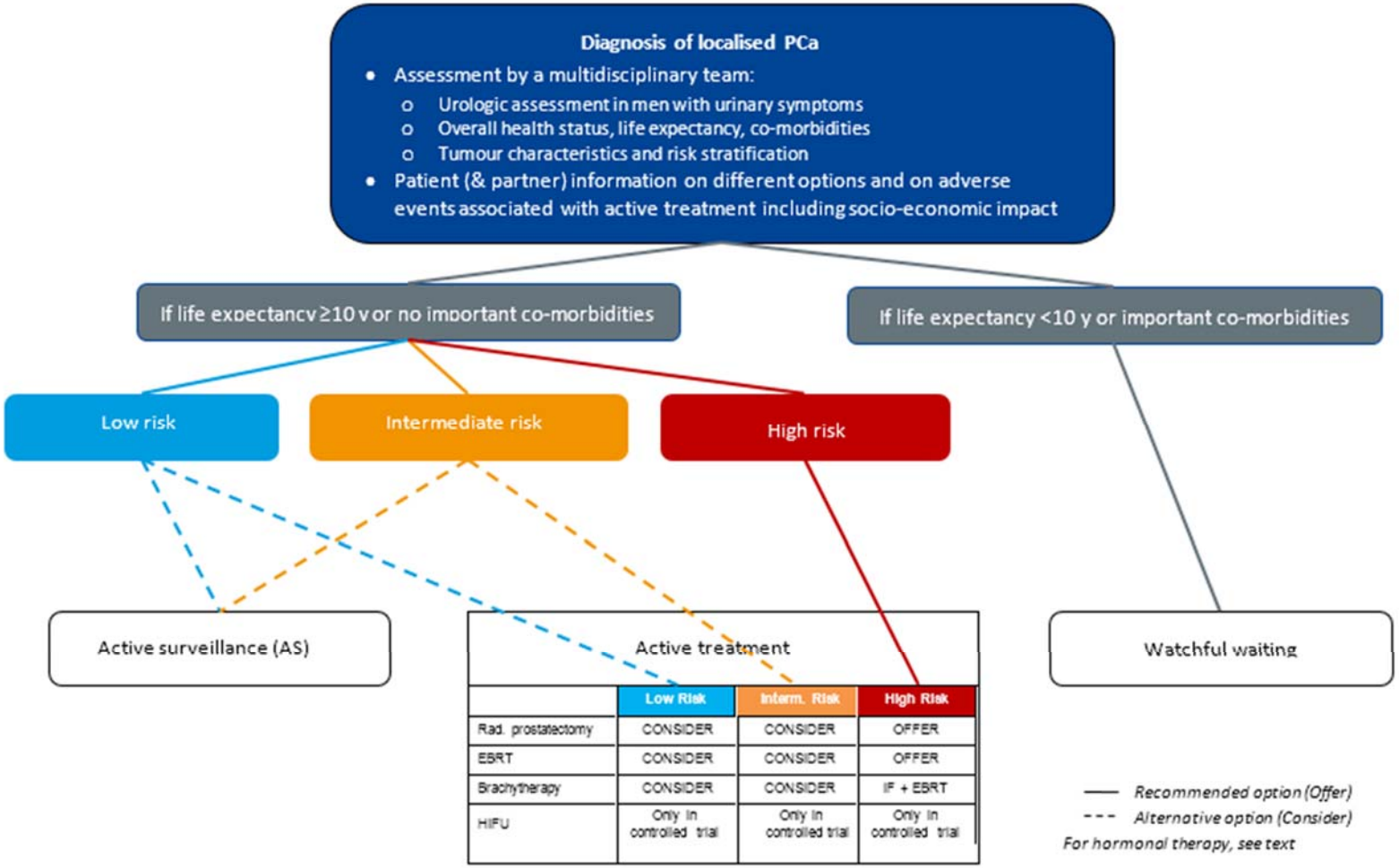
2.3. High Intensity Focused Ultrasound (HIFU)

Recommendation	Level of evidence	Strength of recommendation
Consider HIFU as a treatment option in men with localised prostate cancer only in the context of controlled clinical trials.	Very low	Weak

2.4. Hormones in mono-therapy

Recommendation	Level of evidence	Strength of recommendation
Do not offer hormonal therapy as a unique treatment modality to men with localised prostate cancer (any risk level).	Moderate	Strong

3. ALGORITHM



	Low Risk	Interm. Risk	High Risk
Rad. prostatectomy	CONSIDER	CONSIDER	OFFER
EBRT	CONSIDER	CONSIDER	OFFER
Brachytherapy	CONSIDER	CONSIDER	IF + EBRT
HIFU	Only in controlled trial	Only in controlled trial	Only in controlled trial

Recommendations related to watchful waiting and active surveillance are discussed in part-1 of this guideline[1]
EBRT: External beam radiotherapy
HIFU: High Intensity Focused Ultrasound

4. METHODOLOGY

This guideline was developed using a standard methodology. Details about KCE and its guideline development methodology are available at https://kce.fgov.be/content/kce-processes. Several steps were followed. Firstly, after identifying the topics of key interest following a web survey,[1] clinical questions were developed and the inclusion and exclusion criteria were defined in collaboration with members of the Guideline Development Group. Secondly, a systematic literature review was conducted (including a search for recent, high quality guidelines). Thirdly, on the basis of the results of the literature review, recommendations were formulated and graded according to the GRADE approach.

4.1. The Guideline Development Group (GDG), authors, external experts and stakeholders

This guideline was developed as a result of collaboration between multidisciplinary groups of practising clinicians, KCE researchers, patient representatives and patients. At the start of the production of the guideline, the "College voor Oncologie/Collège de médecins d'Oncologie" submitted a list of experts that were considered as potential members of the GDG (Appendix). The GDG as defined in the present guideline consists of persons from this list who attended at least one GDG meeting. All of them were granted co-authorship.

Some of the persons on the original list did not attend any meeting but provided feed-back by e-mail. They are named "external expert". Their comments were discussed at the GDG meetings and incorporated in the minutes of the meetings.

Stakeholders are persons that were not involved in the guideline development and who were asked at the end of the guideline production process to provide their opinions on the clarity, completeness and acceptability of the recommendations, and on the potential barriers and facilitators related to the use of this guideline. A stakeholder can be a healthcare professional, a patient representative, a patient or his partner.

The composition of the GDG, and persons involved as expert or stakeholder, is listed in Appendix.

Guideline development and literature review expertise, support, and facilitation were provided by the KCE.

The roles assigned to the GDG were:

- To define the clinical questions, in close collaboration with the KCE Expert Team and stakeholders;
- To identify critical and important outcomes;
- To provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed;
- To provide feedback on the content of the guideline;
- To provide judgement about indirectness of evidence;
- To provide feedback on the draft recommendations.

4.2. Clinical research questions

Each of the clinical questions about interventions was re-formulated according the PICO framework (Participants–Intervention–Comparator–Outcomes) as listed in Table 1.

Table 1 – Research questions and PICOs

Research question	Description
Research question 1	***What is the clinical performance of prostatectomy compared with other radical therapies?***
Population	Men with localised prostate cancer, of any age, with no prior treatment
Intervention	Radical prostatectomy
Comparator	Conventional radiotherapy, brachytherapy, HIFU
Outcomes	Overall survival, disease-specific survival, biochemical disease-free survival, time until next intervention, side effects, quality of life, cost
Research question 2	***What is the clinical performance of conventional radiotherapy compared with other radical therapies?***
Population	Men with localised prostate cancer, of any age, with no prior treatment
Intervention	Conventional radiotherapy
Comparator	Prostatectomy, brachytherapy, HIFU
Outcomes	Overall survival, disease-specific survival, biochemical disease-free survival, time until next intervention, adverse events, quality of life
Research question 3	***What is the most effective radical prostatectomy method for prostate cancer: retro-pubic, transperineal, laparoscopic or robot-assisted laparoscopic radical prostatectomy?***
Population	Men undergoing radical prostatectomy for clinically localised prostate cancer (covariates – surgical volume)
Intervention	Open prostatectomy (including retropubic and transperineal approaches), laparoscopic prostatectomy, robot-assisted laparoscopic radical prostatectomy
Comparator	Each other
Outcomes	Overall survival, disease-free survival, biochemical disease-free survival, treatment-related morbidity (transfusion rate), treatment-related mortality, adverse events (incontinence, erectile dysfunction), health-related quality of life, operating time, in-patient hospital stay, positive margins
Research question 4	***What is the impact of dose escalation in external beam radiotherapy?***
Population	Men with localised prostate cancer, of any age, with no prior treatment
Intervention	Conformal radiotherapy standard dose
Comparator	Conformal radiotherapy escalated dose
Outcomes	Overall survival, disease-specific survival, biochemical disease-free survival, time until next intervention, adverse events, quality of life
Research question 5	***How does hypofractionated radiotherapy compare with conventionally fractionated radiotherapy?***
Population	Men with localised prostate cancer, of any age, with no prior treatment
Intervention	Hypofractionated radiotherapy

Research question	Description
Comparator	Conventionally fractionated radiotherapy
Outcomes	Overall survival, Disease-specific survival, Biochemical disease-free survival, Time until next intervention, Adverse events, Quality of life
Research question 6	***What is the clinical performance of brachytherapy versus other radical therapies?***
Population	Men with localised prostate cancer, of any age, with no prior treatment
Intervention	Brachytherapy
Comparator	Radical prostatectomy, conventional radiotherapy, HIFU
Outcomes	Overall survival, disease-specific survival, biochemical disease-free survival, time until next intervention, adverse events, quality of life
Research question 7	***Is the combination of brachytherapy with external beam radiotherapy more effective than either method alone for localised prostate cancer?***
Population	Men with localised prostate cancer. Risk subgroups: low, intermediate, high
Intervention	High dose rate brachytherapy (HDR-BT) plus external beam radiotherapy (EB-RT) Low dose rate brachytherapy (LDR-BT) plus external beam radiotherapy (EB-RT)
Comparator	HDR-BT alone EB-RT alone LDR-BT alone
Outcomes	Overall survival, disease-free survival, biochemical disease-free survival, treatment-related morbidity, treatment-related mortality, health-related quality of life
Research question 8	***What are the efficacy and side-effects of HIFU in the primary treatment of localised prostate cancer?***
Population	Men with localised prostate cancer (who do not opt for active surveillance)
Intervention	Focal/whole-gland-HIFU focal / whole-gland-HIFU in primary therapy
Comparator	Other radical treatment options: conventional radiotherapy, radical prostatectomy, cryotherapy
Outcomes	Overall survival, prostate-cancer-specific-survival, disease progression, (early and late) adverse events, patient reported outcomes
Research question 9	***What are the efficacy and side-effects of hormonal therapy as primary and sole treatment of localised prostate cancer?***
Population	Men with localised prostate cancer (who do not opt for active surveillance)
Intervention	Any type of hormone as primary and unique treatment
Comparator	Active surveillance/watchful waiting and radical treatment options: external beam radiotherapy, radical prostatectomy, cryotherapy
Outcomes	Overall survival, prostate-cancer-specific-survival, disease progression, (early and late) adverse events, patient reported outcomes

4.3. General approach of the guideline production

To verify whether high-quality recent guidelines that address the clinical research questions are available, our standard guideline development process starts with a search for existing guidelines produced by other institutions. If such guidelines are available, their recommendations are adapted to the local Belgian context according to the ADAPTE methodology (www.adapte.org).[5]

If no high-quality, recent guidelines in line with the defined PICOs are available, the general approach is to search for systematic reviews. For each research question a search for systematic reviews is conducted in MEDLINE, Embase and The Cochrane Library (Cochrane Database of Systematic Reviews, DARE and HTA database). In case a recent high quality systematic review is available a search for primary studies published after the search date of the review is performed in MEDLINE and Embase. When no systematic review is available a search for primary studies is to be performed in those databases. Members of the guideline development group (GDG) are also consulted to identify additional relevant evidence that may have been missed by the search.

4.4. Search for existing practice guidelines

4.4.1. Search strategy

The subject to be searched included all three risk categories of localised prostate cancer and the following treatment modalities: 1) radical prostatectomy (RP): open and laparoscopic, 2) radiotherapy: conformal (CRT), intensity modulated radiotherapy treatment (IMRT), interstitial radiation implants (brachytherapy), 3) high intensity focused ultrasound (HIFU), 4) hormonal: androgen deprivation therapy (ADT) and 5) other therapies such as cryotherapy and immunotherapy.

In February 2013 we performed a search for existing guidelines produced by other institutions in order to verify whether high-quality recent guidelines that address our clinical research questions were available. This search was carried out in several databases (the National Guideline Clearinghouse, NICE, SIGN, and G.I.N.) and websites of oncologic organisations. Guidelines published in Dutch, English, French or German after 01/01/2005 were selected. Details are provided in Appendix.

Subsequently, an electronic search for guidelines was performed using Medline (Ovid) following the procedure described in the KCE process book (https://kce.fgov.be/nl/content/wetenschappelijke-process-notes). The following MeSH terms and text words were used in combination: "prostatic neoplasms"[MeSH], prostate cancer and therapy associated to a filter to retrieve guidelines published since 2005 (Appendix).

After exclusion of duplicates, 22 guidelines were found on specific websites. Two reports on HIFU (KCE 2008, IQWIG 2006) were not considered because they are health technology assessment reports and not clinical guidelines. Two hundred fifty six publications were retrieved on Medline (Ovid). Based on title and abstract and after exclusion of 5 duplicates, 23 publications were selected.

Finally, a hand search for guidelines on localised prostate cancer was performed on Medline, resulting in 18 additional hits.

Thus, a total of 63 guidelines or best practice documents published since 2005 were retrieved.[4, 6-63] Screening based on title with 2 researchers excluded 33 references because they were out of scope, duplicates or had been updated. The NICE 2011 was merely a consultation document concluding to the need for an update. The resulting 30 guidelines were listed by topic and chronology (Appendix).

4.4.2. Quality appraisal

A rapid quality appraisal using the AGREE tool II (www.agreetrust.org) was performed on these 30 guidelines by 2 independent researchers. The following items from Domain 3 of the AGREE instrument (“Rigour of development”) were appraised: question 7 (“systematic methods were used to search evidence”), question 8 (“the criteria for selecting evidence were clearly described”) and question 10 (“methods for formulating recommendations were clearly described”). Each researcher rated the guidelines individually and results were discussed in face to face meetings. Scores were summed up, with a possible minimum of 6 and a maximum of 42. Guidelines with a score over 24 were included for complete evaluation (Appendix). The 15 guidelines that fulfilled this criterion are highlighted in the corresponding list (Appendix). In a final step, they were fully appraised by 2 independent team members (Appendix) and results were compared and discussed face to face.

The selected guidelines were ranked based on the final scores and search dates (Table 2). According to our assessment the NICE 2008 guideline was the highest quality.

Table 2 – Quality ranking of existing guidelines

Guideline	Search date	Overall AGREE quality score
NICE 2008[50]	June 2007	7
EAU 2012[4]	November 2011	5.5
ARAGON INSTITUTE 2008[59]	Search date unclear Released: Sept 2008	5.5
AUA 2007[52]	April 2004	4.5
IKNL 2007[64]	Not exactly defined: Jan 2003 - Jan 2005	4.5

4.4.3. Source Guideline: the 2014 NICE Prostate Cancer Guideline

Given the high quality of the NICE 2008 guideline and the fact that it addressed most of our research questions, we contemplated to adapt the recommendations from this particular guideline to the Belgian context.[5]

Since we knew that NICE was preparing an update of its 2008 guideline, we decided to await the publication of the corresponding "Drafts for consultation" before proceeding with the adaptation process. In April 2011, the National Collaborating Centre for Cancer (NCC-C) was asked by NICE to conduct a review of the 2008 Prostate Cancer Guideline CG58[50] to determine if an update was required. This review was conducted in accordance with the NICE guideline development process[65] and required a search for new evidence, using versions of the original search strategies, seeking views of past Guideline Development Group members, and of feedback on the 2008 guideline post publication. Based on these sources of information, the NCC-C prepared a review proposal suggesting the following areas of CG58 required updating: the optimum combination of hormones and radiotherapy for patients with localised or locally advanced prostate cancer, the most effective technique for performing radical prostatectomy, the effectiveness of high dose rate brachytherapy in combination with external beam radiotherapy.[47]

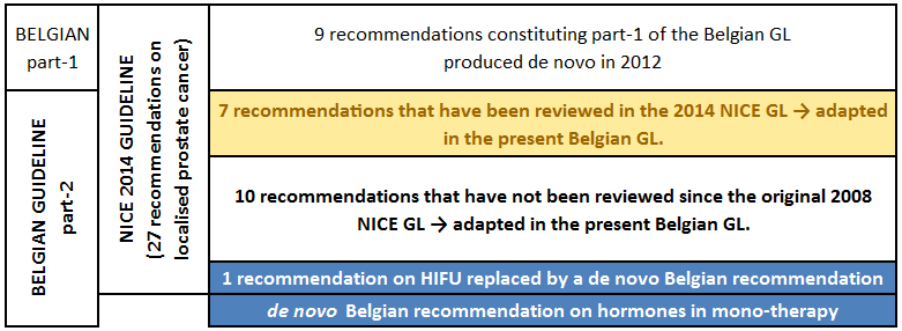
The NCC-C then was commissioned by NICE to produce the new guideline. GDG meetings were held between February 2012 and May 2013. During each meeting clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. In May 2013 searches were updated and re-run, thereby ensuring that the latest relevant published evidence was included.[66]

NICE's "Drafts for consultation" became available in July 2013,[67, 68] together with a full disclosure of the Evidence Review.[69] We used those documents to prepare the present Belgian guideline. In January 2014 NICE eventually published the new guideline ("CG175").[66, 70] As far as the items of interest for the present Belgian guideline are concerned, only minor changes appeared in the final document as compared to the drafts. Further in this text, we will refer to these source documents as the "NICE 2014 guideline".[66, 69, 70]

The NICE 2014 guideline encompasses a broad spectrum of recommendations for the diagnosis and treatment of prostate cancer, including the management of adverse effects of radical treatment, metastatic cancer and palliative care. The chapter on localised prostate cancer includes 27 recommendations related to treatment as such. Nine of them are primarily related to active surveillance and watchful waiting (AS/WW) and are the topic of part-1 of the Belgian guideline.[1] The remaining 18 recommendations are related to clinical questions that are relevant for the present Belgian guideline and were considered adequate for adaptation to the Belgian context. For 7 of them the evidence that supported the 2008 recommendations was extensively reviewed in de NICE 2014 guideline. They are marked as [2014]. For 11 recommendations NICE considered a review of the evidence provided in 2008 not to be necessary. Those recommendations are marked as [2008] or [2008, amended 2014], the latter notation indicating that the evidence was not reviewed since 2008, but changes were made to the wording that (slightly) changed the meaning.

The structure of the Belgian prostate cancer guideline in comparison with NICE's guideline is depicted in Figure 2.

Figure 2 – Composition of the Belgian as compared to NICE's guideline



"Belgian part-1" refers to Mambourg et al.[1]

4.5. Search for evidence for *de novo* recommendations

Two items were considered of particular importance by the Belgian GDG: one implies the use of HIFU and the other considers the use of hormones in mono-therapy in localised prostate cancer. Since the underlying evidence for HIFU was not updated in the 2014 NICE guideline, and the use of hormones in mono-therapy was out of scope for NICE, we performed a review ourselves in order to produce *de novo* recommendations on these items.

4.5.1. Study design and date limits

The inclusion criteria for the study design were: systematic reviews (meta-analyses), RCTs, and observational studies (the latter for HIFU only). Exclusion criteria for the study design were: editorials, narrative reviews and cadaver/animals studies. Studies presented as conference abstract only for HIFU were excluded. The study was not taken into account for the final recommendations when no full-text was available. Articles in Dutch, English, French, Spanish and German were included. Only studies with a sample size of at least 50 participants were included.

A hierarchical approach was followed. First, we searched for recently published systematic reviews (SR). For HIFU the start date was from February 2008, i.e. the search date of a rapid assessment of HIFU for prostate cancer performed by the KCE in 2008[71] and the end date was 15 May 2013. For hormonal mono-therapy the search start date was 2008 for SRs and no defined start date for RCTs; the end date was 22 January 2014. Second, the selected evidence synthesis was updated by a search for all relevant primary studies published after the search date of the selected SR, if any.

To be included a systematic review had to:

- address the research question;
- evaluate at least one of the selected (critical and important) outcomes;
- include RCTs or observational studies;
- search MEDLINE and at least one other electronic database;
- include an assessment of risk of bias of each primary study which included at least the three following main items: concealment of allocation, blinded outcome assessment and completeness of follow-up (preferably summarised in a table).

To be included a primary study had to:

- be an RCT or an observational study (the latter for HIFU only);
- address the research question;
- evaluate at least one of the selected (critical and important) outcomes.

The whole process of the studies selection is documented in Appendix.

4.5.2. Databases

The following databases were included in the literature search: the Cochrane Database of systematic reviews (http://www.cochrane.org), Medline (http://www.ncbi.nlm.nih.gov/pubmed) and Embase (http://www.embase.com/). The ClinicalTrials.gov website was consulted to retrieve all ongoing trials. Further information about ongoing research was obtained by contacting study authors and organisations. Members of the GDG were also consulted to identify relevant evidence that might have been missed during the search process.

4.5.3. Search strategy

A combination of appropriate MeSH terms and free text words was used as documented in Appendix.

Studies were screened on title and abstract by two independent researchers with inclusion and exclusion criteria extracted from the PICO. In case of doubt a third researcher was consulted. First, the titles and abstracts of the identified studies were checked and irrelevant studies were excluded. In a second step, the remaining papers were screened on a full-text basis by the same researchers. In case no full-text was available, the study was not taken into account for the final recommendations. Hand searching of additional articles was performed on the basis of reference list in all the selected studies.

4.5.4. Quality appraisal

The quality appraisal was performed by two independent researchers previously trained in order to obtain consensus for appreciation of the publications.

- Systematic reviews were assessed using the AMSTAR checklist[72] (http://amstar.ca/Amstar_Checklist.php).
- The quality appraisal of RCTs for therapeutic interventions was performed using the "Cochrane Collaboration's tool for assessing risk of bias" (see Appendix). For each criterion the definitions as described in the Cochrane Handbook were used. If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes). In the end, each study was labelled as low risk of bias, unclear risk of bias or high risk of bias according to the criteria described in the Cochrane Handbook.
- Study limitations in observational studies were evaluated using GRADE criteria: failure to develop and apply appropriate eligibility criteria (inclusion of control population); under- or overmatching in case-control studies; selection of exposed and unexposed in cohort studies from different populations; flawed measurement of both exposure and outcome; differences in measurement of exposure (e.g., recall bias in case-control studies); differential surveillance for outcome in exposed and unexposed in cohort studies; failure to adequately control confounding; failure of accurate measurement of all known prognostic factors; failure to match for prognostic factors and/or lack of adjustment in statistical analysis, and incomplete follow-up. Observational studies without control group were considered low quality.

The tools used for the quality appraisal are reported in Appendix. The results of the quality appraisal are presented in Appendix.

4.5.5. Data extraction

For each systematic review, the search date, publication year, funding, included studies and main results were extracted. For observational studies, the following data were extracted: publication year, country, setting, funding, sample size, population characteristics, duration of follow-up, study intervention and outcomes. For RCTs and longitudinal studies, the following data were extracted: publication year, study population, study intervention, and outcomes.

Data extraction was performed by one researcher, checked by another and entered in evidence tables using standard KCE templates. Any disagreements were resolved by discussion or, if required, by a third party.

All evidence tables are reported in the Appendix.

4.6. Grading the quality of the evidence (Level of Evidence – LoE)

4.6.1. Quality of evidence of de novo recommendations

The strength and quality of the evidence supporting a recommendation is provided according to "GRADE for guidelines". The quality of evidence is classified into 4 categories: high, moderate, low, and very low (Table 3).[73, 74] The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation.

Table 3 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem et al.[73]

The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating was initially considered to be of high level (Table 4). The rating was then downgraded if needed based on the judgement of the different quality elements (Table 5). Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.[74]

Observational studies were by default considered low level of evidence (Table 4).[74] However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
   a. Large, i.e. RR >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level
   b. Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels
2. All plausible confounders: all plausible confounding from observational studies or randomised trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient: The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used to downgrade the quality rating are summarised in Balshem et al.[73] Decisions on downgrading with -1 or -2 points were based on the judgement of the assessors. Reasons for (not) downgrading were summarized in the GRADE profiles.[73]

Table 4 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomised trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Source: Guyatt et al.[74]

Table 5 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention.

	Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

4.6.2. Quality of evidence of adapted recommendations

Our strategy for grading the quality of the evidence supporting the recommendations that we adapted from NICE was as follows.

A level of evidence (LoE) was attributed only to recommendations for which NICE executed a recent evidence review, i.e. those labelled "[2014]".[70] However, it appears that NICE attributes a LoE for each outcome separately, which sometimes leads to several LoE per recommendation. For the sake of clarity, and in accordance with the GRADE procedure, we granted one single LoE per recommendation, corresponding to the quality of evidence (as reported by NICE) for the outcome that we considered most critical.

We did not attribute a LoE to NICE "[2008]" recommendations, first since no recent evidence update was performed, and second since NICE did not apply the GRADE grading system in 2008.

4.7. Formulation of recommendations

The "recommendations to be adapted to the Belgian context" in a first step were copied verbatim (word for word) from the NICE 2014 guideline.[70] For "*de novo* recommendations" a first draft of the recommendations was prepared by a small working group based on the retrieved evidence. This working group consisted of the KCE researchers and a few GDG members (the president and in some cases a specialist on a given topic) who made suggestions via e-mail. This first draft of all recommendations was, together with the underlying evidence, circulated to the GDG members 2 weeks prior to the face-to-face meetings that took place on September 18th 2013, February 4th 2014 and March 18th 2014.

All invited GDG members also received in advance a list of each draft recommendation and were asked to indicate on a 5-point Likert scale their level of agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' 'somewhat disagree', '3' 'unsure', '4' 'somewhat agree', and '5' 'completely agree' (they could also answer 'not applicable' if they were not familiar with the underlying topic). If they disagreed with the recommendation (score '1' or '2'), they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation or the strength of the clinical recommendations. The summary score tables are provide in Appendix.

During the meetings, the wording of the recommendations could be altered if deemed necessary, e.g. to increase its clarity. More profound changes could also be made if the evidence provided by NICE was judged differently by the Belgian GDG, although major changes were allowed only if supported by important new evidence. Every such decision was notified and reported in a separate paragraph preceding the recommendation under the heading "Belgian GDG assessment". Based on the discussion during the meetings, a second draft of recommendations was prepared and once more circulated to the guideline development group for final approval on February 4th, March 18th, and May 5th, 2014.

Translations into Dutch and French were prepared by respective native Dutch or French speaking KCE researchers. Those were also discussed at the May 5th, 2014 meeting (stakeholders and GDG members).

4.8. Grading the Strength of Recommendation (SoR)

The strength of recommendation (SoR) was assigned by using the GRADE system (Table 6).

Table 6 – Strength of recommendations according to the GRADE system

Strength	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice).*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice).*

Source: Andrews et al.[75]

The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences, and estimated cost (resource utilization) (Table 7). For this guideline, no formal cost-effectiveness study was conducted. Factors that affect the strength of a recommendation are reported according to Andrews et al.[75]

Table 7 – Factors that affect the strength of a recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted.

Sources: Schünemann et al. and Guyatt et al.[76, 77]

A strong recommendation implies that most patients would want the recommended course of action. A weak recommendation implies that the majority of informed patients would want the intervention, but many would not.[75] Specifically, a strong negative recommendation means the harms of the recommended approach clearly exceed the benefits whereas a weak negative recommendation implies that the majority of patients would not want the intervention, but many would. In the case of a weak recommendation, clinicians are especially required to spend adequate time with patients to discuss patients' values and preferences. Such an in-depth discussion is necessary for the patient to make an informed decision. This may lead a significant proportion of patients to choose an alternative approach. Fully informed patients are in the best position to make decisions that are consistent with the best evidence and patients' values and preferences. For policy-makers, a strong recommendation implies that variability in clinical practice between individuals or regions would likely be inappropriate whereas a weak recommendation implies that variability between individuals or regions may be appropriate, and use as a quality of care criterion is inappropriate.[75]

We offer the suggested interpretation of "strong" and "weak" recommendations in Table 8.

Table 8 – Interpretation of strong and conditional (weak)* recommendations

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

** the terms "conditional" and "weak" can be used synonymously*
Source: Andrews et al.[75]

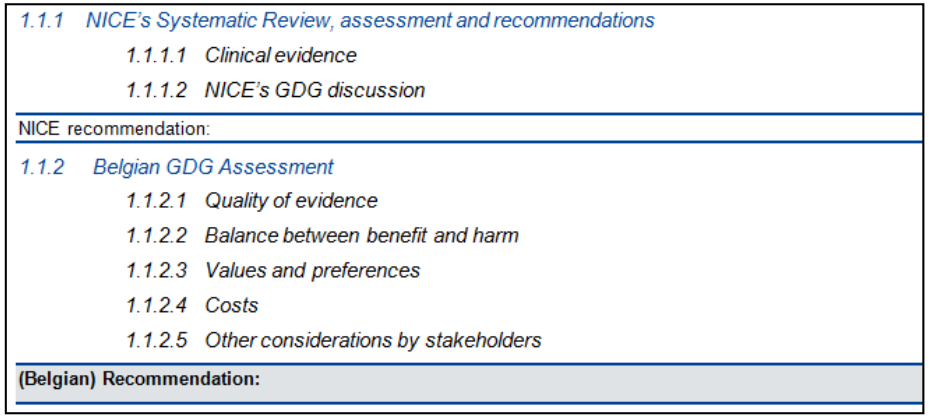
For strong recommendations, the English "offer" is used in the formulation of the recommendation.[68] In the translated version of the recommendations, "to offer" is translated in Dutch as "aanbieden", "gebruiken", "moeten toegepast worden", "moeten aangewend worden" and in French as "proposez". For weak recommendations, "to consider" is translated in Dutch as "overwegen" and in French as "envisagez".

The procedure to attribute a Strength of Recommendation (SoR) explained above was used in both the *de novo* and adapted recommendations. This means that the GDG could decide to change the SoR that was attributed by NICE to a given recommendation, e.g. because of local (Belgian) differences in "values and preferences".

4.9. Lay-out of chapters describing the recommendations adaptation process

Figure 3 shows the general editorial lay-out of the chapters that describe how NICE's recommendations were adapted to the Belgian context (Chapters 6 and 7). The text in the paragraphs "NICE's Systematic review, assessment and recommendations" is mostly copied word-for-word from the NICE 2014 Full Guideline[66] and the NICE 2014 Evidence Review.[69] For tables of evidence and references to specific scientific papers, the reader is referred to these source documents.

Figure 3 – Editorial lay-out of chapters describing the recommendations adaptation process (chapters 7 and 8)



4.10. External review and stakeholders involvement

On May 5th 2014, a "stakeholders meeting" took place. As defined earlier, stakeholders are persons that were not involved in the guideline development. A stakeholder can be a healthcare professional, a patient representative, a patient or his partner. Stakeholders were requested to review the draft recommendations on clarity, completeness and acceptability and on the potential barriers and facilitators related to the use of the guideline. They were also asked to check whether important considerations from a patient's perspective had been missed in the formulation of the recommendations and whether we needed to add information that could assist patients in making clear choices when doctors discuss treatment options with them.

GDG members and external experts were invited to this meeting as well. Their role was mainly to answer questions from stakeholders and to discuss new scientific evidence if any. They could decide during this meeting whether modifications or clarifications as proposed by stakeholders had to be made in the recommendations.

Declarations of interest were formally recorded for any person involved in this guideline development process.

All persons invited to the meeting were sent the full text scientific report 2 weeks before. They were asked to score each recommendation on a 5-point Likert scale indicating their level of agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' 'somewhat disagree', '3' 'unsure', '4' 'somewhat agree', and '5' 'completely agree' (they could also answer 'not applicable' if they were not familiar with the underlying evidence). If they disagreed with the recommendation (score '1' or '2'), they were asked to provide an explanation supported by appropriate evidence. In Appendix, an overview of these scores is provided.

Discussions and textual adaptations resulting from the stakeholders meeting were reported in the full text of the guideline (Figure 3).

4.10.1. Healthcare professionals

The following professional associations were invited to delegate one or more members to a stakeholders meeting on May 5th, 2014: Domus Medica, SSMG, Belgische Vereniging voor Urologie, Société Belge d'Urologie, and ABRO-BVRO (radiotherapists). In case a member was interested to participate but was unable to be present at the meeting, he was invited to provide written comments. Seven healthcare professionals accepted our invitation to evaluate the clinical recommendations: 4 urologists, 2 radiotherapists, and 1 oncologist.

4.10.2. Patient representatives

The prostate cancer patient association "Us Too Belgium – Wij Ook vzw – Nous Aussi" was contacted to invite patients or patient representatives to take part in the stakeholder meeting. Three persons accepted to co-operate: 2 patients and 1 patient representative.

4.11. Final validation

On May 23th 2014, the guideline was discussed ("external assessment") with 2 independent external experts (Nicolas Mottet – urologist, and Guy Soete - radiotherapist) who were asked to validate the scientific content of the guideline. Minor textual changes could still be made if deemed necessary by these experts and were reported in the full text.

At last, on May 27th, the final guideline was submitted to CEBAM, the Belgian Centre for Evidence Based Medicine, for a validation based on the AGREE II instrument.

5. EXTRACT FROM PART-1 OF THE BELGIAN PROSTATE CANCER GUIDELINE

The GDG considered it vital to remind the user of this guideline on a number of recommendations formulated in part-1 of the Belgian prostate cancer guideline.[1, 2] These recommendations always have to born in mind and discussed with men presenting with a localised prostate cancer in whom a treatment with curative intent is considered.

- Before any treatment decision can be made, an assessment of the patient's overall health status, his individual life expectancy and co-morbidities should be undertaken during a multidisciplinary team meeting.
- A patient, eligible and opting for a strategy with curative intent, should be informed about commonly accepted initial managements with regards to his health status, individual life expectancy and tumour risk category. Commonly accepted initial managements include at least active surveillance, radiotherapy (external beam and interstitial), and radical prostatectomy. The estimated benefits and harms of each intervention should be explained and discussed with the patient.
- In patients with localised prostate cancer (any risk category) and an individual life expectancy <10 years or with important co-morbidities watchful waiting with palliative intent is recommended.
- In patients with low risk localised prostate cancer, eligible and opting for a strategy with curative intent, active surveillance should be considered as a management option, taking into account patient preferences and health conditions related to urinary, sexual, and bowel function. Men with low-risk localised prostate cancer must be informed that at the present time there is no demonstrated benefit within 10 to 12 years for immediate treatments as opposed to observation.

6. RECOMMENDATIONS ON PATIENT INFORMATION

6.1. Sexual dysfunction after treatment

6.1.1. NICE's Systematic Review, assessment and recommendations

The text below is copied from the NICE 2014 Full Guideline (pages 240-241)[66] and the NICE 2014 Evidence Review (pages 719-744).[69] For tables of evidence and references to specific scientific papers, the reader is referred to these source documents that are freely accessible on-line.

Sexual dysfunction is a very common side effect of all treatments for localised prostate cancer. Sexual dysfunction is a general term which includes loss of libido, erectile dysfunction, loss of ejaculatory function, infertility and psychosexual issues. The risk of loss of sexual function has an important influence on the decisions which men and their partners make about treatment for prostate cancer. Although there is evidence that, following an initial loss of erectile function, spontaneous improvements will occur in a proportion of men without specific intervention, most men who undergo radical treatment for prostate cancer experience erectile dysfunction and this is a cause of distress for the majority.

In a systematic review of 14 observational studies between 64% and 100% of men were potent before radical prostatectomy (RP).[78] The reported rates of post-operative potency were 18% to 76% for bilateral nerve-sparing RP, 13% to 56% for unilateral nerve-sparing RP and 0% to 34% for non-nerve sparing RP.

A review of case estimated that between 33% and 82% in patients with erectile dysfunction (ED) after RP are distressed.[79] A prospective study compared QoL and satisfaction with sex life in men after RP who did and did not use treatment for ED.[80] ED treatment was not associated with improved overall quality of life, but was associated with improved sexual items on the QoL scale.

NICE recommendations

- Prior to radical treatment, warn men and, if they wish, their partner, that radical treatment for prostate cancer will result in an alteration of sexual experience, and may result in loss of sexual function. [2008, amended 2014]
- Warn men and, if they wish, their partner, about the potential loss of ejaculation and fertility associated with radical treatment for prostate cancer. Offer sperm storage. [2008, amended 2014]

6.1.2. Belgian GDG Assessment

This part of NICE's guideline not only recommends that specific information should be given to patients but it also discusses potential treatments of erectile dysfunction induced by prostate cancer treatment. The latter aspect however is beyond the scope of the present Belgian guideline.

The GDG members agree that "sexual experience" covers more than only erectile function and therefore agree with NICE's wording "sexual experience". They propose to replace "warn" by "inform" and "radical treatment" with "any active treatment" because any intervention on the prostate may have an impact on the sexual experience of a patient.

The GDG members emphasised the importance of mentioning the potential fertility problems. Offering sperm storage however may pose ethical questions and practical problems (not available everywhere). Thus, the wording "discuss the possibility" is used in the Belgian recommendation instead of "offer".

6.1.3. Stakeholders considerations

One patient-stakeholder stresses the importance to differentiate in the guideline between sexual activity and reproductive ability, the latter being less relevant in most prostate cancer patients. The GDG members felt this message was clear in the proposed recommendation and did not change it.

The need to "discuss the possibility of sperm storage" with patients was a matter of concern for several stakeholders since it is obvious that most prostate cancer patients (median age ±70 years) have no longer reproductive ambitions. It was decided to keep the draft recommendation unchanged.

Recommendations

- **Prior to prostate cancer treatment, inform men and, if they wish, their partner that any active treatment may result in an alteration of sexual experience and may result in loss of sexual function (strong recommendation).**
- **Inform men and, if they wish, their partner about the potential loss of ejaculation and fertility associated with active treatment for prostate cancer. Discuss the possibility of sperm storage (weak recommendation).**

6.2. Urinary and gastro-intestinal adverse effects of treatment

6.2.1. NICE's Systematic Review, assessment and recommendations

The text below is copied from the NICE 2014 Full Guideline (pages 241-243)[66] and the NICE 2014 Evidence Review (pages 745-760).[69] For tables of evidence and references to specific scientific papers, the reader is referred to these source documents that are freely accessible on-line.

Urinary incontinence of all types has been reported after prostate cancer treatment. Radical prostatectomy can especially lead to stress incontinence, which may be temporary or permanent. Incontinence may be a problem after brachytherapy and external beam radiotherapy, in those men who have also had a trans-urethral resection of the prostate. The severity of the symptoms is very variable as is the degree to which this bothers individual men. Treatments for incontinence include physical (pelvic floor muscle re-education, bladder retraining), medical (drug therapy) or surgical (injection of bulking agents, artificial urinary sphincters or perineal sling).

NICE recommendations

- Offer men experiencing troublesome urinary symptoms before treatment a urological assessment. [2008]
- Warn men undergoing radical treatment for prostate cancer of the likely effects of the treatment on their urinary function. [2008]

6.2.2. Belgian GDG Assessment

This part of NICE's guideline not only recommends that specific information should be given to patients but it also discusses potential treatments of urinary incontinence induced by prostate cancer treatment. The latter aspect however is beyond the scope of the present Belgian guideline.

The first of those recommendations is self-evident in the eyes of the GDG. However, GDG members mentioned real-world cases where the patient was referred for prostate biopsy without prior urological assessment, e.g. after a prostate cancer was detected by chance on an MRI or PET scan. Therefore, this recommendation still needs to be mentioned in guidelines. Urinary symptoms may not directly be related to prostate cancer (most localised prostate cancers are asymptomatic) but may be due to benign prostate hypertrophia (BPH). Signs or symptoms (obstruction, hematuria) may need to be treated or further explored before tackling the cancer.

Urinary incontinence and erectile dysfunction are common side-effects of surgery or radiotherapy. However, other complications can ensue and compromise quality of life, sometimes needing hospital admission or surgical intervention. They include urinary or rectal bleeding, infection of the urinary or lower gastrointestinal tract and recto-urethral fistulae. An increased prevalence of secondary malignancies in men who received radiotherapy has also been reported.[81] The latter complication has been extensively documented in the NICE guideline. Less severe and sometimes temporary problems include pain, diarrhoea, pollakisuria and constipation. The patient representative in the GDG stresses that physicians are legally obliged to inform patients also on rare potential adverse events. The GDG members agreed to keep the more general description on urinary function in the recommendation. They proposed to make the following textual changes in NICE text: "inform" instead of "warn" and "active" instead of "radical" treatment since any intervention on the urinary tract may induce adverse effects.

A patient representative within the GDG stressed the importance of documenting in the present report the risk for major adverse events related to radical treatment. Clear data are not available. A specific definition for post-RP incontinence has not been established. In addition, urinary control has been shown to improve over time following surgery, and therefore an assessment of urinary control also depends on the timing relative to surgery.

Reported rates of incontinence following radical prostatectomy have ranged from 5% to 72%. The heterogeneous manner in which incontinence may be defined has been in large part responsible for these widely disparate figures. For example, 72.2% and 65.6% of men in separate series reported any degree of incontinence after radical prostatectomy on a patient self-reported questionnaire, whereas 39% and 33%, respectively, reported incontinence requiring protection.[82]

NICE formulated a separate recommendation on the occurrence of colorectal cancer after radiotherapy. There was consensus within the GDG meeting to mention this adverse event in one single recommendation combined with other urinary and gastro-intestinal side effects since it appears to be very rare and is supported by limited solid evidence.

6.2.3. Stakeholders considerations

It was stressed that there were no known adverse events strictly associated to the stomach and therefore "gastro-intestinal" in the draft recommendation was changed to "digestive".

Another stakeholder insisted that radical prostatectomy had little impact on intestinal function. The GDG referred to the temporary defecation problems that might occur in the early postoperative phase.

An external assessor wanted the risk of incontinence to be explicitly stressed.

Recommendations

- **Offer a urological assessment to men who experience urinary symptoms before treatment of their prostate cancer (strong recommendation).**
- **Inform men and if they wish, their partner of the potential effects on urinary function, particularly the risk of incontinence, and digestive function associated with active treatment for prostate cancer (strong recommendation).**

6.3. Colorectal cancer after radiotherapy

6.3.1. NICE's Systematic Review, assessment and recommendations

The text below is copied from the NICE 2014 Full Guideline (pages 234-240)[66] and the NICE 2014 Evidence Review (pages 696-712).[69] For tables of evidence and references to specific scientific papers, the reader is referred to these source documents that are freely accessible on-line.

6.3.1.1. Clinical evidence

Observational studies suggest a geometric mean raw incidence of 1.3% (range 0.1% to 6.6%) for the development of any secondary bowel cancer in men who have received radiotherapy for prostate cancer. Observational studies which report rates of secondary colon or rectal cancer in men who have received radiotherapy for prostate cancer suggest geometric mean raw incidences of 1.1% (range 0.4% to 3.4%) and 0.5% (range 0.0% to 8 8.3%) respectively. The meta-analysis included six studies and found a significantly higher risk of developing colorectal cancer following radiotherapy compared with no radiotherapy in men previously diagnosed with prostate cancer (RR:1.27; 95% CI 1.23-1.31). The risk was also significantly higher for colon and rectal cancers individually (RR: 1.09; 95% CI 1.05-1.13 and RR:1.15; 95%CI 1.10-1.21 respectively). However, there was wide variability between studies after 94%CI.

Six of the studies specifically looked at the increased risk of bowel cancer in those who had received EBRT alone for prostate cancer. There was no significant difference in the risk of any colorectal cancer or specifically colon cancer in those treated with EBRT compared to no radiotherapy ($p \geq 0.1$). However, there was still a significantly increased risk of rectal cancer following EBRT when compared with no radiotherapy (RR: 1.21; 95% CI 1.11-1.32).

In many of the studies a latency period was used to exclude the possibility of synchronous colorectal cancers, which varied considerably in length between studies. The exclusion of any studies which included secondary bowel cancers occurring within 5 years of diagnosis or treatment resulted in no significant increase in risk of any colorectal or colon cancer following radiotherapy ($p \geq 0.1$), but a significant increase in risk of rectal cancer for those treated with radiotherapy (RR:1.18; 95% CI 1.07-1.31).

Only one observational study allowed calculation of the incidence rate per person-year for any secondary bowel cancer in men who have received radiotherapy for prostate cancer; this was found to be 1,169 cases/100 000 person-years.[83] The geometric mean incidence rates for colon and rectal cancer were found to be 220 cases/100 000 person-years (range 188 and 248 cases/100 000 person-years) and 102 cases/100 000 person-years (range 52 and 220 cases/100 000 person-years) respectively. This compares to 190 and 105 cases/100 000 person-years in the no-radiotherapy control groups respectively. From these figures, if 1000 men were screened for 10 years we might expect to detect around 32 colorectal cancers in those undergoing radiotherapy, compared to around 30 colorectal cancers in those not undergoing radiotherapy.

6.3.1.2. NICE's GDG discussion

Quality of the evidence

The evidence for all reported outcomes was assessed by GRADE as very low quality. The GDG noted that the evidence came from a limited number of studies, some of which had small sample sizes. It was also noted that some of the evidence was only available in abstract form.

Trade-off between clinical benefits and harms

The GDG acknowledged that the evidence had shown men who had received radical radiotherapy for prostate cancer were at increased risk of developing secondary bowel malignancy, although the magnitude of this increase risk was uncertain. Since radiotherapy is only one of several potential treatment options for prostate cancer, the GDG agreed it was important to ensure men were given this information to assist them in making informed decisions about what treatment to have.

The GDG noted that the available evidence did not contradict the recommendation from CG58[50] that men with symptoms of radiation-induced enteropathy should be investigated to exclude inflammatory bowel disease or malignancy of the large bowel and to ascertain the nature of the radiation injury. They therefore agreed to retain this recommendation because the GDG did not want patients to assume that symptoms were simply related to radiotherapy late effects. The GDG also agreed it was important to retain the recommendation from CG58 that caution should be exercised with anterior wall rectal biopsy following brachytherapy because of the risk of perforation.

Trade-off between net health benefits and resource use

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG considered there would be no additional costs associated with informing patients of the increased risk of cancer, but potential cost savings from removing the recommendation to perform regular flexible sigmoidoscopy.

NICE recommendation

- Tell men that there is a small increase in the risk of colorectal cancer after radical external beam radiotherapy for prostate cancer. [2014]

6.3.2. Belgian GDG Assessment

An increased prevalence of secondary malignancies in men who received radiotherapy has been extensively discussed by NICE. NICE attributed a separate recommendation on the occurrence of colorectal cancer after radiotherapy. There was consensus in GDG meeting to mention this adverse event in one single recommendation combined with other urinary and digestive side effects as discussed above.

6.3.3. Stakeholders considerations

It was agreed to incorporate this item in a previous recommendation ("Inform men undergoing active treatment for prostate cancer of the likely effects of the treatment on urinary and digestive functions").

6.4. Socio-economic aspects of radical treatment

A patient representative among the GDG members insisted to add an additional recommendation on the socio-economic aspects of active prostate cancer treatment. Every cancer has a social impact (e.g. cost of treatment, appointments during work hours) and the costs related to the treatment of adverse events (diapers, erectile dysfunction treatment) can influence a patient's choice.

The management of adverse events associated with radical prostate cancer treatment was beyond the scope of the present guideline. Nevertheless, the GDG agreed to add this recommendation because it might affect a patient's decision whether or not to accept active treatment. The GDG remarks that no proper Belgian cost data are available per adverse event.

Recommendation

- **Discuss the socio-economical impact of radical treatment, including potential professional disability and out-of pocket expenses, related to the management of adverse treatment effects (strong recommendation).**

7. RECOMMENDATIONS ON RADICAL TREATMENT

The Belgian GDG confirms that surgery and radiotherapy (external beam and brachytherapy) constitute standard radical treatment strategies for patients eligible and opting for a strategy with curative intent. Ablative techniques such as HIFU, cryotherapy and Tookad (Pd-bacteriopheophorbide-Mediated Photodynamic Therapy) have not been extensively studied so far and their potential role in the treatment of prostate cancer is presently unclear. In the present guideline, an up-to-date evidence review on the use of HIFU is undertaken whereas the other ablative techniques were beyond the scope of this project.

7.1. Radical surgery and radical radiotherapy

Radical prostatectomy involves removal of the entire prostate gland and seminal vesicles. Surgery has been traditionally performed by an open retropubic or perineal approach. The risks associated with surgery include incontinence, erectile dysfunction and the chance of involved surgical margins. Recently, laparoscopic or robotically assisted techniques have shortened in-patient stays and reduced blood loss. Radical prostatectomy is a major operation that is typically only offered to fitter men without co-morbidities.[69]

External beam radiotherapy is the most common treatment in the UK for men diagnosed with localised prostate cancer. It might be combined with a period of hormonal therapy, and is given in daily fractions over 4–8 weeks as an outpatient. The side effects of this treatment can include alteration in urinary and bowel function and erectile dysfunction.[68]

7.1.1. NICE's Systematic Review, assessment and recommendations

The text below is copied from the NICE 2014 Full Guideline (pages 175-179)[66] and the NICE 2014 Evidence Review (pages 446-472).[69] For tables of evidence and references to specific scientific papers, the reader is referred to these source documents that are freely accessible on-line.

7.1.1.1. Clinical evidence

Radical prostatectomy

Evidence comes from a randomised trial comparing radical prostatectomy and watchful waiting in men with localised, well to moderately-well differentiated prostate cancer.[84, 85] Overall mortality, within 10 years of follow-up, was lower in men treated with prostatectomy than in those managed with watchful waiting: 27.0% versus 32.0% respectively.[84] Similarly, the rate of death from prostate cancer within 10 years of follow-up was lower in the prostatectomy group than in the watchful waiting group (9.6% vs. 14.9% respectively). Erectile dysfunction and urinary incontinence however were significantly more likely in the prostatectomy group.[85]

Two small randomised trials compared prostatectomy with radiotherapy in men with locally advanced prostate cancer[86] and in those with clinically localised prostate cancer.[87] The applicability of the trials is limited due to methodological problems[86, 87] and use of adjuvant and neoadjuvant hormonal therapy in all patients.[86]

Radical radiotherapy

No randomised trials comparing external beam radiotherapy with watchful waiting were found. Evidence about outcomes after external beam radiotherapy comes from observational studies, or from randomised trials comparing radiotherapy techniques. A systematic review included 26 retrospective observational studies (17,018 patients) and reported outcomes after conventional external beam radiotherapy.[88]

7.1.1.2. NICE's GDG discussion

There is no strong evidence for the benefit of one treatment over another. Relatively little health gain is required for these interventions to become demonstrably cost-effective.

NICE recommendations

- Offer radical prostatectomy or radical radiotherapy to men with intermediate-risk localised prostate cancer. [2008]
- Offer radical prostatectomy or radical radiotherapy to men with high-risk localised prostate cancer when there is a realistic prospect of long-term disease control. [2008]

7.1.2. Belgian GDG Assessment

7.1.2.1. Quality of evidence

According to NICE's review, the evidence base for radiotherapy is less clear than for surgery. Randomised trials comparing radiotherapy with watchful waiting/active surveillance, or comparing surgery and radiotherapy are not available. Generally accepted radical treatments with curative intent include radical prostatectomy, external beam radiation therapy, and brachytherapy. The use of high frequency focused ultrasound therapy (HIFU) appears to be less documented than radiotherapy (cf. separate *de novo* recommendation). Because of those uncertainties, the GDG preferred to more broadly refer to "radical treatment", instead of specifying "radical prostatectomy or radical radiotherapy" such as NICE did.

In the 2014 NICE guideline, the PIVOT trial was not discussed since its focus was on an issue for which no literature update was envisaged.[89] The PIVOT trial is a multicenter RCT comparing radical prostatectomy versus observation for men with localised prostate cancer. They had to be less than 76 years of age with an expected life expectancy of more than 10 years, and judged to be medically and surgically fit for RP. They were randomly assigned to radical prostatectomy (RP) or observation and followed through January 2010. Patients included had new (diagnosed within the past 12 months) biopsy proven clinically localised prostate cancer (T1-T2, NxM0). Radical prostatectomy did not significantly reduce all-cause mortality (HR 0.88: 0.71 to 1.08; p=0.22). Radical prostatectomy did not significantly reduce prostate cancer mortality (HR 0.63: 0.36 to 1.09; p=0.09). A pre-planned subgroup analysis was performed. Among men with low-risk tumours (n=296), radical prostatectomy increased not significantly all-cause mortality (HR 1.15: 0.80 to 1.66). Among men with intermediate-risk tumours (n=249), radical prostatectomy reduced significantly all-cause mortality (HR 0.69: 0.49 to 0.98). Among men with high-risk tumours (n=157), radical

prostatectomy reduced not significantly all-cause mortality (HR 0.40: 0.16 to 1.00).

Intermediate risk localised prostate cancer covers a broad spectrum of the disease, making it presently impossible to formulate a general recommendation in those patients. Therefore, and corresponding with part-1 of this guideline,[1] this NICE recommendation has been changed, replacing "offer" in NICE's recommendation to "consider". Moreover, according to the GDG, "consider" implies a stronger patient involvement in the decision making.

The GDG extensively discussed the case where a multidisciplinary team proposes to a patient active surveillance, which the patient cannot accept, e.g. because he is not able to cope with "further living with a cancer in his body". It was concluded to add this extra recommendation: "Consider radical treatment with curative intent in men with localised prostate cancer who prefer radical treatment over active surveillance".

The addition of "... when there is a realistic prospect of long-term disease control" in NICE's recommendation appears superfluous to the Belgian GDG, and therefore was deleted.

7.1.2.2. Balance between benefit and harm

There is no strong evidence for a benefit of one treatment modality over another although the overall evidence base is stronger for surgery than for radiotherapy.

7.1.2.3. Values and preferences

The GDG considered it vital to remind the user of this guideline on a number of recommendations formulated in part-1 of the Belgian prostate cancer guideline. A patient, eligible and opting for a strategy with curative intent, should be informed about commonly accepted initial managements with regards to his health status, individual life expectancy and tumour risk category. Commonly accepted initial managements include at least active surveillance, radiotherapy (external beam and interstitial), and radical prostatectomy. The estimated benefits and harms of each intervention should be explained and discussed with the patient. In patients with localised prostate cancer (any risk category) and an individual life expectancy <10 years or with important co-morbidities watchful waiting with palliative intent is recommended.[1]

7.1.2.4. Costs

No further comments.

7.1.2.5. Other considerations by stakeholders

The recommendation related to the active treatment of patients who decline active surveillance was debated in the stakeholders meeting. It was proposed to add that this recommendation was only intended for low-risk patients. It was however decided to make no changes since this recommendation may also address some patients with intermediate risk cancer or patients.

A stakeholder suggested that patients should be given a decision tool to help them make a choice. The GDG responds that there is no generic tool available and that each patient needs an individual approach; this is why it is stated in several earlier recommendations that informing a patient (and his partner) is a duty for the attending physician.

The external assessors considered it vital to once more remind the user of this guideline on a number of recommendations formulated in part-1 of the Belgian prostate cancer guideline:[1, 2]

- In patients with localised prostate cancer (any risk category) and an individual life expectancy <10 years or with important co-morbidities watchful waiting with palliative intent is recommended.
- In patients with low risk localised prostate cancer, eligible and opting for a strategy with curative intent, active surveillance should be considered as a management option, taking into account patient preferences and health conditions related to urinary, sexual, and bowel function. Men with low-risk localised prostate cancer must be informed that at the present time there is no demonstrated benefit within 10 to 12 years for immediate treatments as opposed to observation.

Recommendations

- **In men with localised prostate cancer to whom active surveillance has been proposed, but who decline, consider standard radical treatment with curative intent (i.e. radical prostatectomy, external beam radiotherapy or brachytherapy) (weak recommendation).**

- **In men with intermediate risk localised prostate cancer, consider standard radical treatment with curative intent (i.e. radical prostatectomy, external beam radiotherapy or brachytherapy) (weak recommendation).**
- **In men with high risk localised prostate cancer, offer standard radical treatment with curative intent (i.e. radical prostatectomy or external beam radiotherapy) (strong recommendation).**

7.2. Radical surgery

7.2.1. NICE's Systematic Review, assessment and recommendations

The text below is copied from the NICE 2014 Full Guideline (pages 179-198)[66] and the NICE 2014 Evidence Review (pages 478-522).[69] For tables of evidence and references to specific scientific papers, the reader is referred to these source documents that are freely accessible on-line.

7.2.1.1. Clinical evidence

Overall survival

One study provided very low quality evidence of no deaths following either open (OP) or laparoscopic (LP) (time of follow-up not reported). Three very low quality studies reported the prevalence of death following OP and robot-assisted laparoscopic prostatectomy (RALP) at varying time points with conflicting results (follow-up ranging from 30 days to 1.5 years). Four very low quality studies found no deaths following either LP or RALP (follow-up 3-12 months where reported).

Biochemical disease-free survival

Ten studies provided very low quality evidence of PSA recurrence following LP compared with OP with varying results over a wide range of follow-up durations. Three of these provided comparable data which could be combined in a meta-analysis, which found no significant difference in risk of biochemical recurrence at 12 months following LP compared to OP (p=0.70).

Nine studies provided very low quality evidence of PSA recurrence following RALP compared with OP, again varying in length of follow-up and findings. Three of these provided data suitable for inclusion in a meta-analysis, which found a borderline significantly lower rate of biochemical recurrence at 12 months following RALP. The RR of 0.70 (95% CI 0.50-0.99) that for every 100 patients undergoing prostatectomy, three fewer would experience biochemical recurrence at 12 months if a RALP technique was used.

One very low quality study found no significant difference in PSA recurrence between LP and RALP groups at 3 months.[90] One low quality study found no significant difference at 5 years[91] and one at a mean of 4.1 years.[92] Six studies of very low quality were included in a network meta-analysis in 2010[93] but no evidence of a difference between the two techniques was found. No new studies have been published reporting this information since 2010.

Treatment-related morbidity (transfusion rate)

Eighteen studies provided low quality evidence of a significantly lower rate of blood transfusion in patients undergoing LP compared to OP. Seventeen studies provided data in a format which could be included in a meta-analysis, this found an relative risk (RR) of 0.29 (95% CI 0.19-0.45) suggests that for every 100 patients undergoing prostatectomy, 41 fewer would need a blood transfusion if a laparoscopic technique was used.

Thirteen studies provided low quality evidence of a significantly lower rate of the blood transfusion during and following RALP compared with OP. The RR of 0.29 (95% CI 0.19-0.43) suggests that for every 100 patients undergoing prostatectomy, 11 fewer would need a blood transfusion if a RALP technique was used.

Ten studies provided very low quality evidence of blood transfusion rates in patients undergoing RALP compared with LP; findings varied across the studies. Nine of the studies provided suitable data for a standard meta-analysis, this found no significant difference in blood transfusion rates between RALP and LP (p=0.52). Thirty studies of very low quality were included in a network meta-analysis in 2010 but no evidence of a difference between the two techniques was found.[93] Following restriction of the network meta-analysis to studies at low risk of bias there remained no significant difference. None of the four studies published since 2010 have found a significant difference in blood transfusion rates.

Adverse events (incontinence, erectile dysfunction)

A variety of different definitions and timescales for incontinence and erectile dysfunction were used in the studies, making comparisons difficult. Eleven studies compared incontinence following LP to OP; results were inconsistent. Four studies of very low quality provided data which could be included in a meta-analysis, which found no significant difference in incontinence rates between LP and OP at 6 months (p=0.27). Five studies of very low quality were included in a meta-analysis which found no significant difference in incontinence rates between LP and OP at 12 months (p=0.32). Eight studies compared erectile dysfunction following LP to OP; results were inconsistent. Two studies of very low quality were included in a meta-analysis and found a significantly lower rate following LP compared to OP at 6 months. The RR of 0.74 (95% CI 0.58-0.94) suggests that for every 100 patients undergoing OP, 17 less would experience erectile dysfunction if they had undergone LP. Five studies of very low quality were included in a meta-analysis which found no significant difference in incontinence rates between LP and OP at 12 months (p=0.63).

Seven studies compared incontinence following RALP to OP; results were inconsistent. Two studies of low quality reported incontinence at 6 months following prostatectomy; one of which found a significantly lower rate following RALP compared to OP. Five studies of very low quality provided data which could be included in a meta-analysis, which found no significant difference in incontinence rates between RALP and OP at 12 months (p=0.08). Seven studies compared erectile dysfunction following RALP to OP; results were inconsistent. Four studies of very low quality were included in a meta-analysis and found a significantly lower rate following RALP compared to OP at 12 months. The RR of 0.61 (95% CI 0.41-0.91) suggests that for every 100 patients undergoing OP, 15 fewer would 1 experience erectile dysfunction if they had undergone RALP.

Eight studies of very low quality compared incontinence following RALP to LP. Two of the studies provided data which could be included in a meta-analysis, which found no significant difference in incontinence rates following RALP compared to LP at 12 months (p=0.31). Ten studies of very low quality were included in a network meta-analysis in 2010 but no evidence of a difference between the two techniques at 12 months was found.[93] Neither of the two studies published since then found a significant difference in incontinence 8 at 12 months. Five studies of very low quality compared erectile dysfunction following RALP to LP. One study found higher rates of erectile dysfunction at 3 months following RALP compared to LP, one found higher rates following LP,[94] and two studies reported similar rates. Another study found higher rates of erectile dysfunction at 12 months following LP compared 13 to RALP.[95]

Health-related quality of life

A variety of different tools and timescales for health-related quality of life were used in the studies, making comparisons difficult. Nine studies compared quality of life between patients undergoing LP and OP; results were inconsistent. Two studies of very low quality using the UCLA-PCI could be combined in a meta-analysis and found no significant difference in urinary function, urinary bother, sexual function, or sexual bother at 6 or 12 months. Two studies of very low quality using the SF-36 were included in a meta-analysis and found no significant difference in physical function, role limitation, bodily pain, mental health, or general health perception at 6 or 12 months.

Four very low quality studies compared quality of life between patients undergoing RALP or OP. One study found no significant difference in scores following either open retropubic or perineal prostatectomy compared to RALP in urinary, bowel, hormonal, sexual summary, or sexual function using the EPIC.[96] Another study found VAS-assessed post-operative pain to be significantly higher on the day following OP than following RALP ($p<0.05$).[97] A third study found no significant difference in the proportion of patients meeting their baseline scores in urinary function, urinary bother, sexual function, or sexual bother at 6 months.[98] While another study used the UCLA-PCI and found minimal differences in urinary function, urinary bother, sexual function, and sexual bother scores during 36 months of follow-up.[99]

Four studies provided low quality evidence of a difference in quality of life between patients undergoing RALP and LP. Miller et al. found a significant difference in the physical component of the SF-12 between the two groups at 6 weeks (MD 3.6 95% CI 2.6-4.6) but not the mental component.[100] Ball et al. found a significant difference in the proportion of patients reaching their baseline score of sexual function at 6 months in favour of RALP using the UCLA-PCI, but not in those reaching the baseline score of sexual bother, urinary function, or urinary bother.[98] Berge et al. found no significant difference in urinary function change from baseline between RALP and LP

at 12 or 36 months, or in sexual function at 12 months.[101] Willis et al. found no significant difference in the urinary function summary score or urinary function, urinary bother, sexual function, or sexual bother subscales of the EPIC between RALP and LP at 12 months.[102] However, there was a borderline significant difference in the urinary irritative/obstructive subscale at 12 months (MD -3.1 95% CI -5.9 to -0.3) in favour of LP.

Disease-free survival and treatment-related mortality

These outcomes were not reported by any of the included studies.

7.2.1.2. NICE's GDG discussion

Relative value placed on the outcomes considered

The GDG considered the outcomes of margin status, transfusion rate, length of stay and adverse events to be the most important as they showed clinically important differences between robotic, laparoscopic and open prostatectomy techniques. Disease-free survival and treatment-related mortality were not reported in the evidence.

Quality of the evidence

There was very low quality clinical evidence for margin status and length of stay; very low to moderate quality evidence for transfusion rate and very low to low quality evidence for adverse events.

The GDG noted the following limitations with the clinical evidence: The data were mostly observational and all grouped together rather than separated according to stage. The patient population may have been different in different studies. Differences in the care pathways in non-UK healthcare settings could influence some of the outcomes measured – for example length of hospital stay.

The GDG also noted that the economic evidence came from a published cost-utility analysis. This evidence was assessed as directly applicable with minor limitations but the GDG agreed there was uncertainty around the key clinical input data used. Consequently there was also uncertainty about the conclusions of the economic evidence.

Trade-off between clinical benefits and harms

The GDG considered that robotic surgery was likely to result in less transfusions and a shorter hospital stay compared with other types of surgery. However there could potentially be a need for increased travel as the robots are not available at every centre. It was agreed that the potential benefits outweighed the potential harms.

The GDG noted that the HTA had shown there were significantly less positive surgical margins with robot-assisted prostatectomy compared to laparoscopic prostatectomy. Whilst studies published since the HTA had found no significant difference in positive margin rates between robot-assisted prostatectomy compared to laparoscopic prostatectomy, the GDG noted that this was based on a limited number of studies which had not used the same methodology for ascertainment of positive margin rates. They therefore agreed to put more weight on the results of the HTA.

Due to the uncertainty in the evidence the GDG agreed it was only possible for them to recommend that provision of robotic surgery be considered.

Trade-off between net health benefits and resource use

The GDG noted that the results of the published cost-utility analysis had shown that robotic surgery was cost effective with an ICER of £28 172/QALY. However this was dependent on a minimum of 150 procedures being performed. Therefore the GDG recommended that robotic systems should be based in centres where the caseload is greater than 150 cases per year.

NICE recommendations

- Commissioners of urology services should consider providing robotic surgery to treat localised prostate cancer. [2014]
- Commissioners should ensure that robotic systems for the surgical treatment of localised prostate cancer are based in centres that perform at least 150 radical prostatectomies per year. [2014]

7.2.2. Belgian GDG Assessment

7.2.2.1. Quality of evidence

According to the research performed by NICE there are no studies that reliably compare different radical surgery modalities on their effect on hard clinical endpoints such as disease-free survival and treatment-related mortality. NICE found low to very low quality evidence suggesting that robot-assisted surgery performs better than other approaches on a number of intermediate endpoints (less transfusions and a shorter hospital stay). There is no hard evidence on the superiority of RALP as compared to other surgical techniques.

Furthermore, since NICE's recommendations - in the eyes of the Belgian GDG - is rather a political and organisational statement and not a clinical recommendation, it is considered beyond the scope of the present GL. This issue has been discussed in a previous KCE report.[103]

7.2.2.2. Balance between benefit and harm

There is no hard evidence that the benefit and/or harm of RALP differs from other radical surgical modalities.[3]

7.2.2.3. Values and preferences

In 2009 KCE issued a Health Technology Assessment (HTA) on robot surgery.[103] By then, 20 robotic surgery systems were in use in Belgium, mainly for performing radical prostatectomy. It was concluded that clear advantages of robot-assisted surgery were unproven and were highly dependent on surgical skills and professional experience of the team performing the intervention.

There is no hard evidence available on a volume/outcome relationship for RALP.

7.2.2.4. Costs

The 2009 KCE report[103] included an economic evaluation of robotic surgery. Since no evidence on hard clinical endpoints was available, the calculation of an incremental cost-effectiveness ratio was considered not meaningful. The main cost-drivers of the robot-assistance in surgery are the acquisition cost, maintenance, and the costs of limited re-usable surgical instruments. Considering a $1.7 million capital investment, a 10% maintenance cost and disposables, one robot-assisted radical prostatectomy was calculated in 2008 to lead to an additionally cost of €4070 to €6420 per patient, depending on the hospital volume (300 to 100 cases per year). Depending on the institution, patients were charged an additional out-of-pocket amount ranging between €0 and €1200.

Starting in 2009, a supplement of €1056 per intervention was granted to specified hospitals that performed robot assisted prostatectomies, provided they met a number of organisational requirements and they participated in a nationwide registry. In 2010 this supplement was €1065 and in 2013 it was €1033. In 2013, 24 institutions were certified for obtaining this supplemental reimbursement.

In 2012, the "Independent Mutualities" (Onafhankelijke Ziekenfondsen – Mutualités Libres) issued a report on the cost of prostate surgery in Belgium in 2010.[104] The reimbursed amount of money for a radical prostatectomy was calculated to be on average €5801 for non-laparoscopic assisted procedures and €(6983+1065)=€8048 for robot assisted surgery.

7.2.2.5. Other considerations by stakeholders

Since NICE's documents do not provide sufficient evidence that the benefit and/or harm of RALP differs from that of other radical surgical modalities, the GDG decided not to include NICE's recommendations on RALP in the Belgian guideline.

Some stakeholders questioned whether there was no need to introduce a recommendation on patient information related to RALP since the technique is often used in Belgium. Given the uncertainties surrounding the added clinical benefit of RALP and the cost-effectiveness of the procedure, it was decided to add no specific recommendation on this subject.

7.3. Adjuvant hormonal therapy after radical surgery

Hormonal therapy is sometimes given for several months before radical treatment (neoadjuvant therapy). Hormonal therapy has been used following both surgery and radiotherapy (adjuvant therapy) with the intention of improving survival. The use of adjuvant hormonal therapy after radical prostatectomy has not been updated as part of this guideline.

The side effects of hormonal therapy can be substantial, especially if given for several years, and so the risk/benefit ratio needs to be considered.

7.3.1. NICE's Systematic Review, assessment and recommendation

The text below is copied from the NICE 2014 Full Guideline (pages 263)[66] and the NICE 2014 Evidence Review (pages 844-849)[69]. For tables of evidence and references to specific scientific papers, the reader is referred to these source documents that are freely accessible on-line.

7.3.1.1. Clinical evidence

Evidence comes from three randomised trials[105-107] included in the Kumar and co-workers Cochrane review.[108] Men treated with adjuvant hormonal therapy had significantly better disease free survival at 5 and 10 years after surgery. In meta-analysis there was no difference in overall survival at 5 years after surgery.

In node-positive men, Messing and co-workers reported a significant survival benefit with adjuvant hormone therapy.[106] In the Wirth study, men treated with adjuvant hormonal therapy had significantly lower overall survival at 10 years after surgery, than the standard care group.[107]

The Messing study reported a significant increase in grade 1 and 2 side effects in the adjuvant hormone group.[106] The Wirth study noted that discontinuation due to adverse effects was twice as likely in the adjuvant hormone group.[107]

7.3.1.2. NICE's GDG discussion

There is evidence from randomised controlled trials of a lack of clinical benefit and significant toxicity to support making this recommendation.

NICE recommendation

- Do not offer adjuvant hormonal therapy in addition to radical prostatectomy, even to men with margin-positive disease, other than in the context of a clinical trial. [2008]

7.3.2. Belgian GDG Assessment

7.3.2.1. Quality of evidence

NICE's recommendation does not apply to patients with a pN1 stage cancer (which is beyond the scope of the present GL). However, the GDG wanted this issue to be stressed by adding "with pN0" to the recommendation.

7.3.2.2. Balance between benefit and harm

No further comments.

7.3.2.3. Values and preferences

The GDG considered that the extension of "other than in the context of a clinical trial" should not be mentioned.

7.3.2.4. Costs

No further comments.

7.3.2.5. Other considerations by stakeholders

One stakeholder suggested changing "even to those" in "as well as those". The GDG responded that pN0 and "margin-positives" refer to the same patients.

Recommendation

- **Do not offer adjuvant hormonal therapy in addition to radical prostatectomy to men with pN0, even to those with margin-positive disease (strong recommendation).**

7.4. Radical external beam radiotherapy

Radiotherapy can be delivered to the prostate in two ways; either using external x-ray beams from a linear accelerator or by radiation sources placed directly into the prostate gland (brachytherapy). Radical external beam radiotherapy techniques have evolved to optimise the dose to the tumour while minimising the risks of normal tissue damage. Current examples of such techniques include image-guided radiotherapy (IGRT) and intensity-6 modulated radiotherapy (IMRT).[69]

There are two different radiation sources used in prostate cancer brachytherapy; low dose rate I125 seeds which are implanted and remain in the prostate lifelong (permanent implants) or high dose rate Ir192 delivered using an after loading machine directed into the prostate along implanted plastic tubes which are subsequently removed (temporary implant). Theoretically brachytherapy can deliver a higher dose than external beam radiotherapy as it does not traverse normal tissues to reach the prostate, however it may itself deliver higher doses to the urethra. Possible side effects include alteration in urinary and bowel function and erectile dysfunction.[69]

7.4.1. NICE's Systematic Review, assessment and recommendations

The text below is copied from the NICE 2014 Full Guideline (pages 198-199)[66] and the NICE 2014 Evidence Review (pages 523-623).[69] For tables of evidence and references to specific scientific papers, the reader is referred to these source documents that are freely accessible on-line.

7.4.1.1. Clinical evidence

Radiotherapy dose

Randomised trials have examined dose escalation in conformal radiotherapy for prostate cancer,[109-112] although Pollack et al.[112] only used a conformal radiotherapy boost. There was consistent evidence of improved biochemical progression-free survival in the higher dose groups, at the cost of increased late bowel toxicity. Longer follow-up is needed before overall or disease specific survival can be compared.

Two randomised controlled trials have compared hypofractionated (fractions of 2.6 Gy or more) with conventionally fractionated (2 Gy fractions) radiotherapy in this population, but at doses lower than currently used.[113, 114] One trial reported overall survival, and found no significant difference between groups at a median follow-up of 5.7 years.[114] There was no evidence about the effect of hypofractionation on disease specific survival, but the evidence suggests an increased risk of biochemical failure and acute treatment toxicity with hypofractionated radiotherapy.

Brachytherapy

There were no randomised trials comparing brachytherapy with other radical therapies or with watchful waiting. Systematic reviews of observational studies found insufficient evidence to compare overall and disease specific survival after brachytherapy with that after other radical therapies.[88, 115-117] Evidence from these systematic reviews suggests that, at least for low-risk patients, biochemical recurrence free survival after brachytherapy is equivalent to that after external beam radiotherapy or prostatectomy. Evidence from systematic reviews comparing the toxicity of radical therapies for prostate cancer suggests brachytherapy has a similar adverse event rate to prostatectomy or external beam radiotherapy, but such comparisons are based on evidence from observational studies.[88, 116, 117] Some reports of brachytherapy case series suggest lower rates of impotence and incontinence than seen with surgery or EBRT but higher rates of obstructive and irritative urinary symptoms.

NICE recommendations

- For men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer planned treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage. [2008]
- Offer men undergoing radical external beam radiotherapy for localised prostate cancer a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction. [2008]

7.4.2. Belgian GDG Assessment

7.4.2.1. Quality of evidence

The GDG agrees with the first of these recommendations on radiotherapy and leaves it unchanged.

Recent RCT evidence has provided new insight in hypofractionated radiotherapy.[118] In this study, men with favorable- to high-risk prostate cancer were randomly allocated to receive 76 Gy in 38 fractions at 2.0 Gy per fraction (conventional fractionation intensity-modulated radiation therapy [CIMRT]) versus 70.2 Gy in 26 fractions at 2.7 Gy per fraction (hypofractionated IMRT). The hypofractionation regimen did not result in a significant reduction in biochemical and/or clinical disease failure; however, it could be delivered in 2.5 fewer weeks. Because of this study and additional not yet published studies that confirm this finding, the GDG decided to omit "at no more than 2 Gy per fraction" from NICE's recommendation. The GDG also refers to a previous KCE report on Intensity Modulated Radiotherapy (IMRT).[119]

According to the GDG, there is no need to change the radiation dose proposed by NICE (74 Gy) in response to the dose used in the abovementioned study (76 Gy).

7.4.2.2. Balance between benefit and harm

No further comments.

7.4.2.3. Values and preferences

Hypofractionation allows treating patients over a shorter period of time.

7.4.2.4. Costs

Hypofractionation allows treating patients over a shorter period of time and may reduce cost.[118, 120]

7.4.2.5. Other considerations by stakeholders

The word "planned" seemed redundant to most attendants of the meeting.

One stakeholder suggested to explicitly adding "delivered in fractions ranging from 1.8 to 2.2 Gy". It was concluded to add "using conventional fractionation". This point was discussed again with the external assessors. It is decided not to go into the technical details about the precise fractionation of the radiation doses. Reference was also made to the evolving nature of this therapeutic modality.

Recommendations

- **In men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage (strong recommendation).**
- **In men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer a minimum dose equivalent to 74 Gy, delivered over 7-8 weeks (strong recommendation).**

7.5. Combined external beam radiotherapy and brachytherapy

7.5.1. NICE's Systematic Review, assessment and recommendation

The text below is copied from the NICE 2014 Full Guideline (pages 199-213)[66] and the NICE 2014 Evidence Review (pages 624-637).[69] For tables of evidence and references to specific scientific papers, the reader is referred to these source documents that are freely accessible on-line.

7.5.1.1. Clinical evidence

Clinical question: Is the combination of brachytherapy with external beam radiotherapy more effective than either method alone for localised or locally advanced non metastatic prostate cancer?

Overall survival.

Moderate quality evidence suggests uncertainty about whether overall survival is equivalent or worse in men treated with external beam radiotherapy (EBRT) and high dose rate brachytherapy (HDR-BT) combined when compared to men treated with EBRT alone. The pooled hazard ratio from two randomised trials for all-cause mortality (combined versus EBRT) was 1.44 (95% C.I. 0.87 to 2.40). Very low quality evidence from a meta-analysis of non-randomised studies suggests a survival benefit for combined

EBRT and HDR-BT compared to EBRT alone (HR 0.67; 95% CI 0.58-0.78).[121]

Biochemical disease-free survival.

Moderate quality evidence suggests better biochemical failure-free survival when men are treated with EBRT and HDR-BT combined than when treated with EBRT alone (HR 0.57; 95% CI 0.41-0.79). However this evidence comes from randomised trials that used lower doses in their EBRT-only arms (66 Gy and 50 Gy respectively) than the minimum of 74 Gy recommended in the 2008 NICE prostate cancer guideline. Very low quality evidence from a meta-analysis of non-randomised studies suggests better biochemical failure free survival combined EBRT and HDR-BT when compared to EBRT alone (HR 0.71; 95% CI 0.66-0.76).[121]

A systematic review[122] identified a very low quality, small, observational study,[123] which found no significant difference in biochemical failure-free survival of the two treatment arms at 5 years: 94% versus 87% for EBRT and low dose rate brachytherapy (LDR-BT) and EBRT respectively.

A systematic review identified very low quality evidence of EBRT and LDR-BT versus LDR-BT alone from two small observational studies with conflicting results.[122] Da Silva Franca *et al*.[124] reported better biochemical failure free survival with combined therapy than with LDR-BT alone at 5 years whereas Wong *et al*.[123] found no significant difference.

Low quality evidence suggests uncertainty about whether biochemical failure differs between higher and lower doses of supplemental EBRT. The evidence comes from a single randomised trial in which only 15 men experienced biochemical failure.[125] The resulting confidence intervals (EBRT 40 Gy + LDR-BT versus EBRT 20 Gy + LDR-BT; HR 1.0; 95% CI 0.36-2.76) are wide enough to include the possibility that either treatment option could be superior to the other.

Treatment-related morbidity

There is low quality evidence of uncertainty about the relative rates of gastrointestinal (GI) complications in EBRT+ HDR-BT and EBRT (OR 1.48; 95% CI 0.55-4.01). Gastrointestinal complications were reported in 6% and 4% of men treated with EBRT+HDR-BT and EBRT respectively. There is also low quality evidence of uncertainty about the relative rates of genitourinary (GU) in EBRT+ HDR-BT and EBRT (OR 1.24; 95% CI 0.71-2.17). Genitourinary complications were reported in 22% and 19% of men treated with EBRT+HDR-BT and EBRT respectively.

Very low quality evidence from an observational study found late grade 3 GI and GU toxicity were more likely with EBRT+LDR-BT than with EBRT alone.[123]

A systematic review identified two relevant observational studies which provided uncertainty about the relative rates of late GI complications in EBRT+LDR-BT versus LDR-BT alone (OR 5.31 95% CI 0.73-38.74).[122] For late GU complications there was similar uncertainty (OR 1.08 95% CI 0.49-2.4).

Health-related quality of life

Moderate quality evidence suggests equivalent health-related quality of life following combined EBRT+HDR-BT and EBRT alone. Hoskin *et al*. found average FACT-P scores returned to pre-treatment levels with 6 months of treatment in both the EBRT+HDR-BT and EBRT alone treatment groups.[126] No significant differences in mean FACT scores were found for any of the three domains: general, prostate and Trial Outcome Index (TOI), or in erectile function scores over a 10.5 year follow-up period.[127]

Disease-free survival and treatment-related mortality

These outcomes were not reported by any of the included studies.

7.5.1.2. NICE's GDG discussion

Relative value placed on the outcomes considered

The GDG considered the outcomes of overall survival, disease-free survival, biochemical disease-free survival, treatment-related morbidity, treatment-related mortality and health-related quality of life to be the most important in determining if the combination of high- or low-dose rate brachytherapy with external beam radiotherapy was more effective than either intervention alone for men with localised or locally advanced non-metastatic prostate cancer. The outcomes of disease-free survival and treatment-related mortality were not reported for any of the comparisons of interest. Of the other outcomes, only biochemical disease-free survival and treatment-related morbidity were consistently reported across all comparisons of interest. None of the evidence reported outcomes according to different risk

groups. No evidence was found comparing high-dose rate brachytherapy plus external beam radiotherapy with high-dose rate brachytherapy alone.

Quality of the evidence

For the comparison of high-dose rate brachytherapy plus external beam radiotherapy with external beam radiotherapy alone, the RCT evidence was assessed by GRADE as low quality for the outcome of treatment-related morbidity and moderate quality for the outcomes of biochemical disease-free survival, overall survival and health-related quality of life. A meta-analysis of non-randomised studies was assessed as very low quality for the outcomes of overall survival and biochemical disease-free survival.

For low-dose rate brachytherapy plus external beam radiotherapy compared to both external beam radiotherapy alone and low-dose rate brachytherapy alone, the evidence was assessed by GRADE as very low quality for the outcomes of biochemical disease-free survival and treatment related morbidity. The GDG noted that the control arms in the trials included in the evidence base, used a lower dose of radiotherapy, which had been previously shown to be inferior to that used in current clinical practice. The GDG were therefore aware that there was some uncertainty over the effectiveness of external beam radiotherapy alone compared to the combined treatment, because the trials had used a lower dose of radiotherapy.

Trade-off between clinical benefits and harms

The GDG noted that the evidence comparing high-dose rate brachytherapy plus external beam radiotherapy with external beam radiotherapy alone had shown improved biochemical disease-free survival without an increase in adverse events for the combined treatment. Taking into consideration the uncertainty over the effectiveness of external beam radiotherapy alone (compared to combined treatment), the GDG decided to recommend that high-dose rate brachytherapy plus external beam radiotherapy be considered as a treatment option. The GDG agreed that it was not possible to make recommendations on any other treatment combinations due to the low quality and limited data available.

Trade-off between net health benefits and resource use

The GDG noted that both the base case for the health economic analysis and the sensitivity analysis had shown that combined high-dose rate brachytherapy plus external beam radiotherapy was cost-effective at a willingness to pay threshold of £20 000/QALY.

NICE recommendations

- Do not offer brachytherapy alone to men with high-risk localised prostate cancer. [2008]
- Consider high-dose rate brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer. [2014]

7.5.2. Belgian GDG Assessment

7.5.2.1. Quality of evidence

According to the GDG, there is insufficient data to support NICE's second recommendation in this paragraph, as far as the subgroup of intermediate-risk patients is concerned. The potential benefit of combining different modes of radiotherapy in high-risk patients is addressed in the first recommendation. Therefore the GDG proposes to delete NICE's second recommendation.

7.5.2.2. Other considerations by stakeholders

It appeared that there was confusion about the use of the word "alone" as it was used in the original NICE recommendation on brachytherapy. Indeed it may mean "not in combination with hormonal therapy" or "not in combination with other radiotherapy modalities". Therefore for the sake of clarity "as a unique radiation therapy modality" was added.

Recommendation

- **Do not offer brachytherapy as a unique radiotherapy modality to men with high-risk localised prostate cancer (strong recommendation).**

7.6. Radical radiotherapy combined with androgen deprivation therapy

Hormonal therapy is sometimes given for several months before radical treatment (neoadjuvant therapy). Hormonal therapy has been used following both surgery and radiotherapy (adjuvant therapy) with the intention of improving survival.

Combining hormone therapy and radiotherapy treatments may therefore provide optimal local and distant tumour control, but is only relevant to those patients where radiotherapy alone would not encompass and eliminate the full extent of the prostate cancer. The hormones may be given for a variable length of time and may precede, be given during and for a period following radiotherapy. The optimal timing and overall duration is uncertain.

The side effects of hormonal therapy can be substantial, especially if given for several years, and so the risk/benefit ratio needs to be considered.

7.6.1. NICE's Systematic Review, assessment and recommendation on the combination of external beam radiotherapy and hormones

The text below is copied from the NICE 2014 Full Guideline (pages 264-272)[66] and the NICE 2014 Evidence Review (pages 850-891).[69] For tables of evidence and references to specific scientific papers, the reader is referred to these source documents that are freely accessible on-line.

7.6.1.1. Clinical evidence

Overall survival

Nine studies involving 5994 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus (any) hormone therapy is associated with longer overall survival (HR 1.3 95% CI 1.2-1.41).

Four studies involving 2725 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy followed by hormone therapy is associated with longer overall survival (HR 1.32 95% CI 1.17-1.47).

Three studies involving 2972 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with hormone therapy followed by radiotherapy is associated with longer overall survival (HR 1.25 95% CI 1.12-1.39).

Two studies involving 297 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with neoadjuvant, concomitant and adjuvant hormone therapy plus radiotherapy is associated with longer overall survival (HR 1.72 95% CI 1.25-2.39).

Four studies involving 2533 patients provided moderate quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with similar or longer overall survival (not pooled).

Disease-free survival

Seven studies involving 3892 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with longer disease-free survival (HR 1.49; 95% CI 1.37-1.62).

Four studies involving 2,808 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy followed by hormone therapy is associated with longer disease-free survival (HR 1.48; 95% CI 1.33-1.64).

Two studies involving 993 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with hormone therapy followed by radiotherapy is associated with longer disease-free survival (HR 1.47; 95% CI 1.28-1.68).

One study involving 91 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with neoadjuvant, concomitant and adjuvant hormone therapy plus radiotherapy is associated with longer disease-free survival (HR 2.51; 95% CI 1.32-4.76).

Two studies involving 1469 patients provided low quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with longer disease-free survival (not pooled).

Distant metastases-free survival

Five studies involving 4332 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with longer metastases-free survival (HR 1.63 95% CI 1.43-1.85).

Two studies involving 1360 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy followed by hormone therapy is associated with longer distant metastasis-free survival (HR 1.73 95% CI 1.46-2.06).

Three studies involving 2,972 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with hormone therapy followed by radiotherapy is associated with longer distant metastasis-free survival (HR 1.49 95% CI 1.22-1.82).

Two studies involving 452 patients provided low quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with similar distant metastasis-free survival (not pooled).

Biochemical disease-free survival

One study involving 5903 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy followed by hormone therapy is associated with longer biochemical-free survival (HR 1.62 95% CI 1.39-1.88).

Four studies involving 3,109 patients provided low quality evidence that compared to treatment with radiotherapy alone, treatment with hormone therapy followed by radiotherapy is associated with longer biochemical-free survival (HR 1.65 95% CI 1.48-1.83).

Two studies involving 338 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with neoadjuvant, concomitant and adjuvant hormone therapy plus radiotherapy is associated with longer biochemical-free survival (HR 23 2.53 95% CI 1.75-3.67).

Two studies involving 1139 patients provided low quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with longer biochemical-free survival (not pooled).

Adverse events

Five studies involving 4813 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with comparable rates of adverse events (not pooled).

Two studies involving 2080 patients provided low quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with comparable rates of adverse events (not pooled).

Cardiovascular events

Five studies involving 3988 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with comparable rates of cardiovascular events (not pooled).

One study involving 263 patients provided moderate quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with comparable rates of cardiovascular events (not pooled).

Health-related quality of life

One study involving 1979 patients provided very low quality evidence that compared to treatment with radiotherapy alone, treatment with radiotherapy plus hormone therapy is associated with lower health-related quality of life.

Two studies involving 2,080 patients provided low quality evidence that compared to treatment with hormone therapy alone, treatment with hormone therapy plus radiotherapy is associated with comparable health-related quality of life (not pooled).

7.6.1.2. NICE's GDG discussion

Relative value placed on the outcomes considered

The GDG considered the outcomes of overall survival and metastases-free survival to be the most important as they reflect the likelihood of a patient staying alive. The other outcomes of biochemical disease-free survival, treatment-related morbidity and cardiovascular events were considered to be surrogate end points and therefore of lower importance. Health-related quality of life was also considered to be an important outcome but data was limited and different studies reported different domains of quality of life. As a result the data on quality of life did not provide a comprehensive view of this outcome and the GDG therefore agreed that it was of limited use.

Quality of the evidence

The quality of the evidence was very low to low as assessed by GRADE for both outcomes. The GDG noted that the studies were subject to a number of design limitations that render them at high or unknown risk of bias. They also noted that most of the studies did not analyse the patients according to the risk groups of interest to the GDG (low, intermediate, high and locally advanced) and because of variation in risk group definitions across the studies, it was not possible to conduct a meta-analysis according to risk group.

Trade-off between clinical benefits and harms

Significant differences were found consistently across most outcomes analysed. The GDG noted that the evidence had shown improved survival for patients receiving combination treatment. Whilst side effects were reported there was no evidence of increased treatment-related morbidity, cardiovascular adverse events or decreased quality of life as a result of combination treatment. The GDG considered that the survival benefits, particularly for patients with intermediate and high risk localised disease, outweighed the potential harms.

Trade-off between net health benefits and resource use

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG, based on their clinical experience, was that recommending combination treatment would result in an increased use of radiotherapy resources but it was difficult to assess the extent of this increase. Equally, recommending combination treatment was likely to reduce the requirement for the management of recurrent and metastatic disease.

NICE recommendation

- Offer men with intermediate- and high-risk localised prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone. [2014]

7.6.2. Belgian GDG Assessment

7.6.2.1. Quality of evidence

The place of androgen deprivation therapy in mono-therapy is considered in a *de novo* recommendation in this guideline. The remaining part of this NICE recommendation is further addressed in the next recommendations on the optimal duration of hormone therapy.

7.7. Optimal duration of hormone therapy combined with external beam radiotherapy

7.7.1. NICE's Systematic review, assessment and recommendations

The text below is copied from the NICE 2014 Full Guideline (pages 273-278)[66] and the NICE 2014 Evidence Review (pages 892-906).[69] For tables of evidence and references to specific scientific papers, the reader is referred to these source documents that are freely accessible on-line.

7.7.1.1. Clinical evidence

Overall survival

Five randomised controlled trials provided evidence on the overall survival of men receiving combined hormone therapy and external beam radiotherapy (EBRT) for prostate cancer. Four of these trials provided data which could be included in a meta-analysis, which found low quality evidence of similar overall survival of men treated with long-term (6-28 months) compared to short-term (3-4 months) neoadjuvant and concurrent hormone therapy (hazard ratio of 0.98; 95% CI 0.87-1.11). The fifth trial provided moderate quality evidence of better overall survival in men treated with long-term (36 months) concurrent and adjuvant hormone therapy compared to those treated short-term (6 months). The hazard ratio of 1.42 (95% CI 1.09-1.84) suggests that if hormone therapy were continued after 6 months for a further 30 months, there would be an absolute increase in survival of 5.7% at 5 years, increasing overall survival from 79.1% to 84.8%.[128]

Disease-free survival

Very low quality evidence from two randomised controlled trials suggests uncertainty about the duration of hormone therapy and disease-free survival. In one trial (RTOG 92-02) comparing 4 versus 28 months neoadjuvant and adjuvant hormone therapy, the risk of disease recurrence was significantly lower in those receiving short-term therapy (HR 0.82 95% CI 0.73-0.91).[129] However, the second trial (TROG 96-01), which compared 3 versus 6 months neoadjuvant and concurrent hormone therapy, found the risk of disease recurrence to be significantly lower in those receiving long-term therapy (HR 1.25 95% CI 1.02-1.54).[130]

Metastases-free survival

Three studies provided moderate quality evidence which suggests that men receiving neoadjuvant and concomitant hormone therapy combined with EBRT are at greater risk of developing distant metastases with short-term therapy (3-4 months) than with long-term (6-28 months). Two of these studies provided data which could be included in a meta-analysis, which gave a hazard ratio of 1.66 (95% CI 1.34-2.06), suggesting that if hormone therapy were continued after 3 months for a further 3 months, there would be an absolute decrease in the number of patients developing metastases of 6.5% at 10 years, decreasing the proportion who develop metastases from 17.4% to 10.9% (based on Horwitz et al.[129]).

Biochemical disease-free survival

Low quality evidence from six RCTs suggests that men receiving neoadjuvant & adjuvant hormone therapy combined with EBRT have a greater likelihood of biochemical recurrence with short-term therapy (3-4 months) than with long-term (6-28 months). Five of these studies provided data which could be included in the meta-analysis, which gave a hazard ratio of 1.20 (95% CI 1.08-1.33), suggesting that if hormone therapy were continued after 3 months for a further 3 months, there would be an absolute decrease in the number of patients with biochemical recurrence of 6.6% at 10 years, decreasing the proportion who experience biochemical recurrence from 64.8% to 58.2% (based on Horwitz et al.[129]).

Cardiovascular adverse events

Low quality evidence from two RCTs suggests that cardiovascular events are less likely to occur in men treated with short-term (4 months) neoadjuvant and adjuvant hormone therapy combined with EBRT, than with long-term (28 months) therapy (RR 0.42 95% CI 0.06-2.82). The evidence suggests that for every 100 men treated with short- instead of long-term neoadjuvant and adjuvant hormone therapy when combined with EBRT, there will be 58 fewer cardiovascular adverse events.

Health-related quality of life

Two trials reported moderate-quality evidence on quality of life using the QLQ-C30 tool. The EORTC trial found no significant difference between groups treated with 6 versus 30 months of concurrent and adjuvant hormone therapy for any of the function scales: global health status and quality of life, physical functioning, cognitive functioning, emotional functioning, role functioning, or social functioning ($p \geq 0.1$ for each).[128] Of the symptom scales used, only insomnia ($p=0.006$) reached statistical significance.

However, the TROG 03-04 trial found all outcomes within the functional domain of the EORTC QLQ-C30 tool to be significantly different at both 18 and 36 months (global, role, cognitive, social, emotional and physical). Within the symptoms domain, dyspnoea and fatigue were found to be significantly different at both 18 and 36 months. (In summary: compared with 6 months of androgen suppression, 18 months of androgen suppression causes additional detrimental changes at the 18 month follow-up in some patient reported outcomes scores but not in global quality-of-life scores. However, with the exception of hormone-treatment related symptoms, these differences resolved by 36 months.[131, 132]

A number of ad hoc quality of life questions were also included by the EORTC authors, all of which were scored significantly lower by those treated with short-term (6-month) hormone therapy: hot flushes, enlarged nipples or breasts, swelling of legs, problems passing urine, reduced interest in sex, and reduced sexual activity.

The TROG 03-04 study also provided moderate quality evidence of no significant difference between 6 months and 18 months of neoadjuvant and concurrent ADT using the overall International Prostate Symptom Score (IPSS) at 18 or 36 months ($p<0.01$). However, there was a significant difference in the sexual activity and hormone-treatment-related symptoms domains of the PR-25 tool at both 18 and 36 months.

7.7.1.2. NICE's GDG discussion

Relative value placed on the outcomes considered

The GDG considered the outcomes of overall survival together with metastases-free survival and biochemical disease-free survival to be the most important to identifying the optimal duration of androgen deprivation therapy when combined with external beam radiotherapy, as they reflect the likelihood of a patient staying alive. The GDG also considered treatment related morbidity, in particular cardiovascular adverse events, to be an important outcome as androgen deprivation therapy is associated with morbidity which can be significant. The GDG noted that data on health-related quality of life were limited.

Quality of the evidence

The evidence for overall survival was low to moderate quality as assessed by GRADE. There was moderate quality evidence for metastases-free survival, cardiovascular adverse events and health-related quality of life and low quality evidence for biochemical disease-free survival. The GDG noted that there were a small number of events for some outcomes and also that the studies used lower-dose radiotherapy which is no longer common practice.

Trade-off between clinical benefits and harms

It was noted that the evidence had shown improved metastases free and biochemical disease-free survival with short-term androgen deprivation therapy (combined with external beam radiotherapy), in men with intermediate- and high-risk prostate cancer. This was balanced against an acceptable level of side effects. However the evidence was inconclusive as to the optimal time point to start androgen deprivation therapy (before, during or after radiotherapy).

It was also noted that there was an improvement in overall survival with long term androgen deprivation therapy compared to short term, in men with high-risk disease. Whilst a more serious side effect profile was demonstrated with such long-term androgen deprivation therapy, the GDG agreed that the survival benefits probably outweighed the potential harms. However, the potential harms were felt to be significant enough to warrant a robust discussion of these outcomes with individual patients.

Trade-off between net health benefits and resource use

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG, based on their clinical experience, was that recommending short term androgen deprivation therapy for men with intermediate- and high-risk disease would potentially reduce costs because men with low-risk disease would no longer receive this treatment and it would also shorten the duration of hormone treatment for some men, compared with current practice.

The GDG also agreed that recommending long-term androgen deprivation therapy in men with high-risk disease was already part of current clinical practice and therefore would not represent a change in cost.

NICE recommendations

- Offer men with intermediate- and high-risk localised prostate cancer 6 months of androgen deprivation therapy given before, during or after radical external beam radiotherapy. [2014]
- Consider extending the period of androgen deprivation therapy to 3 years for men with high-risk localised prostate cancer and discuss the benefits and risks of this option with them. [2014]

7.7.2. Belgian GDG Assessment

7.7.2.1. Quality of evidence

Trials that studied the duration of hormone therapy in combination with radiotherapy included patients with locally advanced tumours. The evidence review for this research question is reported in the chapter on “locally advanced cancer” that is beyond the scope of the present Belgian guideline. The level of evidence (LoE) attributed by NICE’s GDG is typically provided separately per outcome as follows: For overall survival LoE was low to moderate; LoE was moderate for metastases-free survival, cardiovascular adverse events and health-related quality of life; LoE was low for biochemical disease-free survival. Since available scientific data did not allow to clearly differentiating the impact of hormone therapy duration in T1-T2 tumours (i.e. the subject of the present Belgian guideline) an overall LoE “low” was assigned to this Belgian recommendation.

The GDG prefers to consider the combined treatment radiotherapy+hormones separately for patients with intermediate and those with high-risk cancer. The duration of androgen deprivation therapy should be limited to a maximum of 6 months for intermediate risk cancer and be longer than 6 months and up to 3 years for high risk cancer. This period should be concomitant with radiotherapy but can start before and/or continue thereafter.

There is no published data yet on prolonged hormone therapy in combination with radiotherapy in intermediate risk patients.

7.7.2.2. Balance between benefit and harm

The aim of limiting the duration of hormone therapy is to avoid adverse effects.

7.7.2.3. Values and preferences

No further comments.

7.7.2.4. Costs

No further comments.

7.7.2.5. Other considerations by stakeholders

There is some discussion among stakeholders about the duration of hormone therapy in intermediate risk cancer. The GDG’s proposal initially was to write “duration of ADT should not exceed 6 months” whereas some stakeholders claimed that it should be 6 months. There seem to be no good trials on this subject. One trial tested 6 months hormone-therapy versus none but it is not known whether a longer or shorter duration is better or worse. The GDG decided to change the formulation into “consider to continue ADT for 6 months”. This item was discussed again by the external assessors. Randomised trials on this subject are only available for ADT during 6 months exactly. No conclusions can be drawn on longer or shorter treatment durations. Therefore, it was decided to change the word “continue” by “give”.

Recommendations:

- **In men with intermediate risk localised prostate cancer treated with radical external beam radiotherapy, consider concomitant androgen deprivation therapy (ADT). Consider to give ADT for 6 months (weak recommendation) (LoE: low).**
- **In men with high risk localised prostate cancer treated with radical external beam radiotherapy, offer concomitant androgen deprivation therapy (ADT). ADT should be continued beyond 6 months and for a maximum of 3 years (strong recommendation) (LoE: low).**

8. HIFU

8.1. Background

In 2008, the KCE published a rapid assessment of HIFU for prostate cancer.[71] It concluded that *"Biochemical disease-free survival for localised prostate cancer treated with HIFU ranges from to 84% at 22 month to 58% at 72 months. Long term data (cancer specific and overall mortality) are needed to establish evidence on efficacy and comparative studies are required to compare the results with standard treatments".*

Our current search for guidelines resulted in two specific recent guidelines on HIFU. The first one[35] by the Cancer Care Ontario group concluded that the use of HIFU could not be recommended in 2010 as an alternative to curative treatment for localised prostate cancer due to lack of RCTs and short follow-up. The second one by NICE[48] in 2012 identified only three good quality studies, each with less than 50 patients and concluded that evidence on efficacy was lacking but that there were no major safety concerns. NICE encouraged further research, especially definition of patient selection criteria and controlled studies.

However, since the NICE recommendation no comparative studies have been completed and published.

We searched websites were clinical trial are registered (http://clinicaltrials.gov and https://www.clinicaltrialsregister.eu). The clinical trial 'Enlight', a prospective case series, sponsored by the makers of Ablatherm (EDAP), involved 12 centres in the United States and Canada. The results were published as abstract only and did therefore not fulfil our selection criteria.[133] A study comparing Sonoblate and brachytherapy (NCT 00770822) was terminated due to lack of inclusions. The results of HIFU compiled from a European registry (@Registry) are included in our selection.[134]

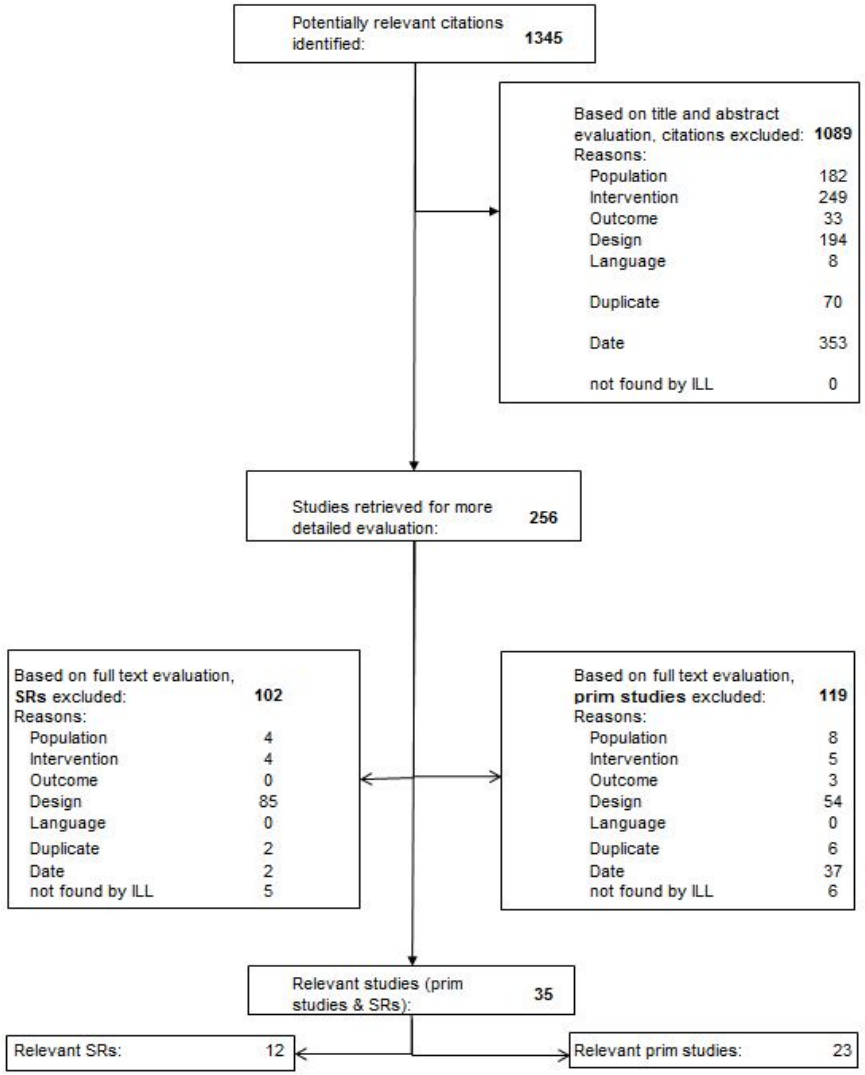
8.2. Literature search results

A global search without lower time limit and up May 15th, 2013 yielded 1345 hits. Two additional abstracts were provided by the GDG. Selection by title and abstract excluded 1089 citation. The remaining 256 references were evaluated on full text (see Figure 4). In a first phase of evaluation on full text, only systematic reviews were searched (from 2008 and onwards) and further analysed. As shown in the flowchart (see Figure 4) 114 references were considered as a review and 142 references were considered as a primary study.

This selection process revealed 12 SRs,[135-146] which were evaluated with the Amstar tool (http://amstar.ca/About_Amstar.php) (see list of included and excluded systematic reviews in appendix).

The list of included primary studies, already selected in the 256 references, was used to further update the review of Warmuth 2010[144]. Only primary studies from 2010 onwards were kept (23 primary studies in total) and primary studies with a sample size smaller than 50 participants were excluded for further analysis (5 studies excluded for small sample size), resulting in 18 primary studies which are described in the results section. Due to the lack of RCTs, the selection of primary studies included only observational studies (mostly case series)

Figure 4 – Flowchart of study selection on HIFU



8.2.1. Systematic reviews

One single systematic review with low risk of bias was identified.[144] The risk of bias of the 12 systematic reviews can be found in appendix. We extracted the specific data concerning HIFU as primary therapy in an evidence table (see appendix). The authors included 18 case series on 2794 patients and analysed outcomes for Ablatherm (A) and Sonoblate (S) separately. Outcomes for efficacy were overall survival, disease specific survival, biochemical disease free survival and negative biopsy rate. Safety outcomes were categorised for urinary tract potency, rectum, pain and quality of life. The critical appraisal according to GRADE was "very low" because all studies were case series with inherent serious limitations and publication biases. Moreover the number of studies was low.

Evidence for overall survival and prostate-cancer specific survival was available in only one trial. Overall survival rates and prostate cancer–specific survival rates were 90% and 100% at 5 yr and 83% and 98% at 8 yr, respectively. Biochemical disease free survival (according to various definitions) was 77% at 5 yr follow-up, 69 % at 7 yr for Ablatherm and 78–84% at 1 yr, 0–91% at 2 yr, 20–86% at 3 yr and 45– 84% at 5 yr for Sonoblate. There was no stratification according to risk category. The reported negative biopsy rate was 80% at 15 months or 78–80% at no specified point in time for Ablatherm and 19–89% at 6 months, 77–84% at 12 months for Sonoblate. Adverse events affecting the urinary tract ranged from 2-58% for Ablatherm and 1-30% for Sonoblate. Erectile dysfunction was reported in 0-18 % after Ablatherm and in 1-39% after Sonoblate treatment. Rectal problems occurred in 0-15% (A) and 0-2% (S). Pain was reported in 1-6 % treated with Ablatherm and in none treated with Sonoblate. Quality of life was evaluated for Ablatherm only and showed small or controversial differences. The authors concluded that high-quality evidence on efficacy and safety is lacking.

8.2.2. Primary studies

Twenty three primary studies published after the closing search date of the SR by Warmuth 2010[144] were identified in the list of relevant publications. All were case-series. Based on the selection criteria that were used in the SR by Warmuth,[144] we excluded 5 studies involving less than 50 subjects: Ahmed 2011[147], Ahmed 2012[148], Barret 2013,[149] El Fegoun 2011,[150] Mishra 2011.[151]

Of the selected 18 studies, the majority (14) used the Ablatherm device[134, 152-164] and only 4 studies reported on the efficacy of the Sonoblate device.[165-168] We report separately on the 2 devices, acknowledging that different generations of instruments were used over the years.

The list of included and excluded studies and the evidence tables can be found in appendix.

8.2.2.1. Ablatherm

Since 2010, 14 case series have reported on a total of 4 699 patients treated by Ablatherm HIFU. These reports originate from European[134], French[152-156], German,[157-160] Italian,[161, 162] Korean[163] and Canadian groups.[164] No comparative studies are available. Study characteristics are illustrated in the summary of evidence (Table 9).

The patient's ages ranged from 48 to 87 years. They were treated for localised prostate cancer, mostly staged as T1 - T3, three studies included T3b and one study included T4. Eight studies mention that HIFU was used because patients declined or were not suited for surgery. Results were not stratified according to the choice made by patient or doctor but according to the risk category (D'Amico classification). Practices varied widely regarding performing prior TURP: from never[164] to always.[154, 157, 159, 161] The percentage of patients receiving prior ADT also varied and was 42% at most.[160] Only 4 reports limited the intervention to 1 HIFU session[159, 160, 163, 164] and it was frequently unclear whether the entire gland was ablated. The follow-up ranged between 6 to 168 months.

Table 9 – Primary studies Ablatherm HIFU

Study	Blana 2012	Boutier 2011	Callea 2010	Crouzet 2010	Crouzet 2011	Crouzet 2013	Ganzer 2013	Maestroni 2012	Netsch 2010	Netsch 2011	Pfeiffer 2012	Pinthus 2012	Ripert 2011	Sung 2012
Country	Europe	France	Italy	France	France	France	Germany	Italy	Germany	Germany	Germany	Canada	France	Korea
Patients n°	356	99	171	803	297	1002	538	74	226	363	189	402	53	126
Patients age, yr, mean or median	Mean: 69.6 (SD 7.2)	Mean: 71.3 (SD 5.7)	Mean: 74.7 (Range: 44-86)	Mean: 70.8 (SD 5.6)	Mean: 71.4 (SD 5.1)	Median: 71 (Range: 48-87)	Mean: 67.7 (±7 yr)	Mean: 72.7 (Range: 65-80)	Mean: 70 (±5.8)	Mean: 69.38 (SD 6.2)	Median: 69.7 (51-82)	Mean: 62.7 (SD 7.5)	Mean: 72.5 (60-79)	Mean: 71 (66-76)
Tumour stage	T1c-T2c	NA	T1-T4	T1-T2	T1-T2	T1-T3	T1a-T3	T1c-≥T2b	T1a-cT3b	T1 or salvage and M0	T1a-cT3b	T1c-T2c	T1a-T2b	T1c-T3b
TURP prior or combined with HIFU, % of pts	57.6	NA	100	90	100	93.7	100	68.9	81.9	100	48.7	none	92.4	89.1 at least
ADT, % of pts	None	NA	NA	None	If prostate vol>35 cm^3	39.1	36.4	28.3	41.1	NA	42	none	none	40.5
Follow-up, mo, mean (range) or median (range)	Median: 32	Mean: 6	Mean: 67.9	Mean: 42 (±33)	Mean: 27 (3-64)	Mean: 76 (2-165)	Mean: 33 (25-168)	Mean: 29.9 (9-40)	Mean: 50 (24-80)	Mean: 50.45 (25-84)	Mean: 52.8 (0.2-79.8)	Median: 24 (6-48)	Mean: 45.4 (16-71)	Median 61.1 (37.2-81)
Type of ablation	Whole	NA	Whole	Whole	Whole	Whole	Whole?	Whole?	Whole?	NA	Whole	Whole?	Whole?	Whole
More than 1 HIFU session	?	?	Y	Y	Y	Y	Y	? primary & salvage	N	Y in 22	N	N	Y	N

The outcomes of interest are described separately. Effects could not be pooled, therefore ranges are indicated for the reported effects. An overview of the results per outcome is presented in Table 10.

The **overall survival rate** was reported at 5 years by one study (86.3%)[160] and ranged from 80 to 89% for over 5 years in 3 other case series.[153, 155, 157] The **prostate cancer specific survival rate** was 100% for a mean follow-up of 27 mo[154], 98.4% at 5 years in one case series[160] and ranged from 96.7 to 99% for over 5 years in the 3 other case series.[153, 155, 157]

Disease free survival was reported according to various definitions. Biochemical disease free survival (BDFS) according to the Phoenix definition (PSA nadir+2ng/ml) within 5 years of follow-up ranged from 64.2 to 85% (4 case series)[153, 154, 162, 169] and from 60 to 79% after 5 years (3 case series).[155, 157, 161] The negative biopsy rate 3 to 6 months after treatment ranged between 63.3 and 84.5% in 6 case series.[152, 153, 157, 160, 162, 169] In these series biopsies were assessed independently of PSA levels and results were not stratified according to risk category.

Combining a negative biopsy, the absence of adjuvant treatment and biochemical recurrence according to the Phoenix definition lowers the range of disease free survival to 64 to 75% within 5 years (2 case series)[134, 154] and 54% after 5 years (1 case series)[134].

Biochemical success or failure rate was stratified against risk category according to the d'Amico classification in 8 reports[153, 155, 157, 160-164] and was uniformly more favourable for the low and intermediate risk category compared to the high risk category. These differences were found statistically significant in 3 case series[153, 160, 164] with success rates ranging from 84% in the low risk to 54.9% in the high risk categories. The extreme values for all 8 case series ranged from 88% biochemical success rate at 5 yrs in the low risk category to 32% at 10 yrs in the high risk category.

Adverse events were categorized into urinary tract, recto-urethral fistula, erectile dysfunction and pain. Scores that were used are the International Index of Erectile Function-15 (IIEF-15), the International Prostate Symptom Score (I-PSS) and in one case a Quality of life score. Life threatening events did not occur.

Erectile dysfunction after the procedure was the most frequent adverse event with reports ranging from 57.7 to 77.7% after HIFU.[155, 157, 161] Two case series compared potency (with or without pharmacological intervention) before and after HIFU.[162, 163] Potency was lost in 63.7%[163] and 75%[162] leading to a total of 90% impotence after HIFU but this author mentions that a nerve sparing technique was not used. IEFF-5 scores were compared pre and post intervention in 3 case series[155, 162, 170] indicating preserved potency in respectively 92.3%, 42.3% (55.6% under 70 yrs old and 25.6% from 70 yrs onwards) and 25%.

Adverse events affecting the urinary tract occurred in 0.7 to 30.9% of patients (7 case series) but the I-PSS score assessing subjective urinary function) remained unchanged pre and post intervention in 2 case series. Bladder outlet obstruction (BOO) occurred in 4 to 51.5%.[155, 157, 158, 160, 162, 163, 167] The obstruction improved over time in two series.[155, 157] Stratifying by risk group shows that BOO developed in 23.5%, 32.9% and 20.6% at low, intermediate, and high risk. The actuarial cumulative incidences of BOO after HIFU at 1, 2, and 3 years were 20.80%, 23.89%, and 24.34% and the rate of primary BOO was significantly different between patients who had undergone TURP the same or within 2 days of receiving HIFU treatment (34.38%) and patients with TURP more than 1 month (17.98%) before HIFU.[158]

Incontinence was scored as light stress incontinence (in 4.0%)[161] or grade 1 (safety pad during the day) (in 2.8 to 26.5%), grade II (2 – 3 pads daily, dry at night)(in 2.8 to 6.3%) and grade III (>3 pads daily and/or wet at night) (in 0.7 to 5%).[154, 155, 157, 160, 162] Overall, transient urinary incontinence occurred in 30.9 to 39.0% of patients.[160, 163] At the final evaluation after a mean follow-up of 61.1 months, in one of these series 6.3% patients (n=8) still reported incontinence (G1 n=6, G2 n=1, G3 n=1).[163]

Seven case series report on recto-urethral fistulas (RUF).[154, 155, 157, 159-162] RUF developed after one HIFU session in 1.6% patients[160]. In another report focusing on this adverse event, 50% of the fistulas also occurred after one session.[159] None of the eight recto-urethral fistulas (2.2%) could be treated conservatively.

Pain seemed minimal: reported in 0.7 to 7.9% of cases in 2 series.[161, 163] A single case series evaluated QoL and found no change after the intervention[154].

Table 10 – Evidence profile Ablatherm HIFU

N° of studies/patients	Study design	Methodological quality	Consistency of results	Directness of evidence	Magnitude of effect, %	Other modifying factors	Level of evidence
Outcome: overall survival rate (at 5 years)							
1/189	Observational, case series	Serious limitations (-1)	Only 1 trial	Direct	86.3%	Publication bias likely	Very low
Outcome: overall survival rate (> 5 years)							
3/2255	Observational, case series, single arm cohort	Serious limitations (-1)	No important inconsistency	Direct	80%-89%		Very low
Outcome: prostate-cancer-specific survival rate (at 5 years)							
1/189	Observational, case series	Serious limitations (-1)	Only 1 trial	Direct	98.4%		Very low
Outcome: prostate-cancer-specific survival rate (> 5 years)							
3/2343	Observational, case series, single arm cohort	Serious limitations (-1)	No important inconsistency	Direct	96.7%-99%		Very low
Outcome: biochemical disease-free survival rate (Phoenix definition, ≤ 5 years)							
4/1021	Observational, case series	Serious limitations (-1)	Important inconsistency	Direct	64.2%-85%		Very low
Outcome: biochemical disease-free survival rate (Phoenix definition, > 5 years)							
3/1896	Observational, case series, single arm cohort	Serious limitations (-1)	Important inconsistency	Direct	60%-79%		Very low
Outcome: disease-free survival rate (Phoenix definition±biopsy+adjuvant treatment, ≤ 5 years)							
2/653	Observational, case series	Serious limitations (-1)	Important inconsistency	Direct	64%-75%		Very low
Outcome: disease-free survival rate (Phoenix definition+-biopsy+ adjuvant treatment, > 5 years)							
1/356	Observational, case series	Serious limitations (-1)	Only 1 trial	Direct	54%		Very low

N° of studies/patients	Study design	Methodological quality	Consistency of results	Directness of evidence	Magnitude of effect, %	Other modifying factors	Level of evidence
Outcome: negative biopsy rate (3-6 months after HIFU)							
6/1818	Observational, case series	Serious limitations (-1)	Important inconsistency	Direct	63.6%-84.5%		Very low
Outcome: adverse events urinary tract							
7/2452	Observational, case series, single arm cohort	Serious limitations (-1)	Important inconsistency	Direct	0.7-30.9%	Lack of precise data	Very low
Outcome: adverse events recto-urethral fistula							
7/2271	Observational, case series, single arm cohort	Serious limitations (-1)	No important inconsistency	Direct	0.4-2.2%	Lack of precise data	Very low
Outcome: adverse events impotency rate/ erectile dysfunction							
2/484	Observational, case series	Serious limitations (-1)	Important inconsistency	Direct	63.7-74.4%	Lack of precise data	Very low
Outcome: adverse events pain							
2/423	Observational, case series	Serious limitations (-1)	No important inconsistency	Direct	0.7-7.9%		Very low
Outcome: IEFF-5							
3/558	Observational, case series, single arm cohort	Serious limitations (-1)	No important inconsistency	Direct	Worsened Preserved potency in 7.7 – 42.3%		Very low
Outcome: IPSS							
2/371	Observational, case series	Serious limitations (-1)	No important inconsistency	Direct	No change		Very low
Outcome: QoL							
1/297	Observational, case series	Serious limitations (-1)	Only 1 trial	Direct	No change		Very low

8.2.2.2. Sonoblate

Since 2010, 4 case series report on a total of 702 patients treated by Sonablate HIFU. These reports originate from Japanese[165-167] and Canadian[168] research groups. No comparative studies are available. Study characteristics are illustrated in Table 11. The patient's ages ranged from 45 to 91 years. They were treated for localised prostate cancer, mostly staged as T1 - T2. One study mentioned that HIFU was used because patients declined or were not suited for surgery. Results were not stratified according to choice by patient or doctor but according to risk category (D'Amico classification). Practices varied widely regarding performing prior TURP: from no one to 29.9% of the patients. The percentage of patients receiving prior ADT also varied and was 65.6% at most. Only in one report more than 1 HIFU sessions were performed and it was frequently unclear whether the entire gland was ablated. The follow-up ranged from 2 to 84 months.

Table 11 – Primary studies Sonoblate HIFU

Study	Elterman 2011	Inoue 2011	Komura 2011	Soji 2010
Country	Canada	Japan	Japan	Japan
Patients n°	95	137	144	326
Patients age, yr, mean	64 (Range 46-91)	70 (Range 50-82)	68.4 (+-7.3)	68 (45-88)
Tumour stage	?	T1-T2	T1c-T2c	T1c-T2b
TURP prior or combined with HIFU, % of pts	0	13	29.9	5.5
ADT, % of pts	10.5	23	43.8	65.6
Follow-up, mo, mean (range)	24	36 (12-84)	47 (2-70)	24
Kind of ablation	?	Whole?	Whole?	Whole avoiding neurovascular bundles
More than 1 HIFU session	N but HIFU as salvage therapy in 7 men	Y	N	N

The outcomes of interest are described separately. Ranges are indicated for the reported effects in Table 12 because effects could not be pooled. Details can be found in the evidence tables (see appendix).

The **overall survival rate** in less than 5 years, reported by two studies,[165, 166] ranged from 96.4% to 98.6%. The **prostate-specific survival rate** was 100% in the same 2 studies. No evidence was reported on overall or prostate-specific survival rate over 5 years.

Biochemical disease free survival rate according to the Stuttgart definition was 85% at 2 yrs[168] and according to the Phoenix definition 67.8% at 5 years[166] and 84%, 64% and 45% respectively for the low, intermediate and high risk categories at 8 yrs.[167] DFSR defined by a combination of Phoenix criteria and negative biopsy was 61.2% at 5 yrs.[166] BDFS (Phoenix) plus negative biopsy and absence of metastases was overall 83.6 % at 3 yrs and 77.8% at 5 yrs.[165] There was a significant difference in the outcome of low and high risk patients ($p<0.05$): at 3 yrs 96.7 % for low risk, 83.9% for intermediate risk and 73.5% for high risk, at 5 yrs 91.3% for low risk, 80.7% for intermediate risk and 61.7% for high risk.

One report stratified results for the presence of urethral stricture (US) and found that it was significantly correlated with biochemical disease free survival (Phoenix definition). At 5 yrs BFSR was 76.7 % in patients with US and 55.8% in patients without US.[166] Biopsies were assessed in 2 case series[165, 166] and were reported to be negative in 72.7 to 91%. This outcome was also better in patients with urethral stricture.

Adverse events affecting the urinary tract were reported by all four studies with a large range for different symptoms occurring overall in 0.7 to 40.3%.[165-168] Urinary stricture occurred in 9%,[168] 10%,[165] 16%[167] and 40.3%[166] but being subclinical in this last study. Recto urethral fistulas could not be detected[165]. Six months after the procedure, 51% of patients reported urinary leakage and 17% clinically significant incontinence.[168] Erectile function was reported by three studies. The number of patients with IIEF score under 7 increased by 37% in the study by Inoue 2011[165]. In another study only 4 additional patients from a group of 52 decreased to a score lower than 11 after HIFU treatments.[168] In the last report 52%, 63% and 78% of the patients, not receiving neo-adjuvant hormonal therapy, were potent at 6, 12 and 24 months after HIFU.[167] Data on pain were lacking but quality of life measured by the FACT-G score improved at 24 months in one study.[167]

Table 12 – Evidence profile Sonoblate HIFU

N° of studies/patients	Study design	Methodological quality	Consistency of results	Directness of evidence	Magnitude of effect, %	Other modifying factors	Level of evidence
Outcome: overall survival rate (< 5 years)							
2/281	Observational, case series	Serious limitations (-1)	No important inconsistency	direct	96.4%-98.6%		Very low
Outcome: overall survival rate (> 5 years)							
No evidence found							
Outcome: prostate-cancer-specific survival rate (< 5 years)							
2/281	Observational, case series	Serious limitations (-1)	No important inconsistency	direct	100%		Very low
Outcome: prostate-cancer-specific survival rate (> 5 years)							
No evidence found							
Outcome: biochemical disease-free survival rate (Phoenix definition, at 5 years)							
1/144	Observational, case series	Serious limitations (-1)	Only 1 trial	direct	67.8%		Very low
Outcome: biochemical disease-free survival rate (Phoenix definition, > 5 years)							
1/326	Observational, case series	Serious limitations (-1)	Only 1 trial	direct	Low risk:84 %, intermediate risk:64%, high risk 45 %		Very low
Outcome: disease-free survival rate (Phoenix definition+ negative biopsy, at 5 years)							
1/144	Observational, case series	Serious limitations (-1)	Only 1 trial	direct	61.2%		Very low
Outcome: disease-free survival rate (Phoenix definition+ negative biopsy > 5 years)							
No evidence found							
Outcome: disease-free survival rate (Phoenix definition+ negative biopsy + free of metastases < 5 years)							
1/137	Observational, case series	Serious limitations (-1)	Only 1 trial	direct	86.3%		Very low

N° of studies/patients	Study design	Methodological quality	Consistency of results	Directness of evidence	Magnitude of effect, %	Other modifying factors	Level of evidence
Outcome: disease-free survival rate (Phoenix definition+ negative biopsy + free of metastases at 5 years)							
1/137	Observational, case series	Serious limitations (-1)	Only 1 trial	direct	77.8%		Very low
Outcome: negative biopsy rate (≥6 months after HIFU)							
2/281	Observational, case series	Serious limitations (-1)	No important inconsistency	direct	72.7%-91%		Very low
Outcome: adverse events urinary tract							
4/702	Observational, case series	Serious limitations (-1)	Important inconsistency	direct	0.7%-40.3%	Lack of precise data	Very low
Outcome: adverse events recto urethral fistula							
1/137	Observational, case series	Serious limitations (-1)	Only 1 trial	direct	0%	Lack of precise data	Very low
Outcome: adverse events erectile dysfunction (IEFF score)							
1/137	Observational, case series	Serious limitations (-1)	Only 1 trial	direct	37%	Lack of precise data	Very low
Outcome: adverse events pain							
No evidence found							
Outcome: IPSS							
No evidence found							
Outcome: QoL							
1/326	Observational, case series	Serious limitations (-1)	Only 1 trial	direct	Significant improvement after 12 mo		Very low

8.3. GDG conclusions

All outcome estimates on efficacy and safety of HIFU are based on uncontrolled case series. There are no direct prospective comparisons with active surveillance or any other type of radical treatment. Moreover baseline characteristics of patients and definitions vary considerable across case series. The GDG members emphasised the limitations of the Phoenix definition for biochemical outcome because of the variable nadir values.

In some of reported case series, HIFU was used in patients who were no candidates or declined radical surgery, in others it was intended as a salvage therapy option in recurrent prostate cancer after radiotherapy failure. Furthermore, in published case series the number of HIFU treatment sessions per patient varies between one and five. Interpretation of results and comparisons between studies are also hampered by the use of different ablation techniques (whole vs. focal), instruments (various generation of Ablatherm and Sonoblate) and additional interventions (TURP, hormonal therapy). MRI-guided HIFU and fusion of the MRI-images with real time ultrasound images during HIFU-treatment may offer better localisation of the region of interest in case of focal treatment. GDG members stress that the technical experience of the HIFU-operator and the appropriate selection of patients is of utmost importance in order to obtain optimal treatment results. The impact of these items on patient relevant endpoints has yet to be shown.

The quality of the evidence of the effectiveness of HIFU in the treatment of localised prostate cancer that presently emerges from the scientific literature has to be graded as very low. The findings based on our updated systematic literature search remain in line with the general conclusions of the 2008 KCE report[71] and the 2012 NICE guideline.[66] At present, good quality evidence is lacking regarding the efficacy of HIFU. In addition, despite a perceived favourable safety profile, side effects on the urinary tract and erectile function are not negligible.

The GDG discussion underscored the current paradox since HIFU treatment is offered as alternative to radical treatment in Belgium (mainly in 2 centres). It was suggested to limit the use of HIFU to experienced centres in the context of controlled trials where whole gland HIFU treatments should be compared to radical prostatectomy/radiotherapy and nerve sparing HIFU to nerve sparing prostatectomy.

8.4. Stakeholders' considerations

The aptness of a recommendation that aims to limit the application of a technique that is already in use to clinical trial conditions is questioned. The reimbursement of HIFU was beyond the scope of the present guideline and would need a full HTA (health technology assessment).

A healthcare professional, member of the GDG, reported that new EAU guidelines were presented at the EAU meeting of April 2014. Under the header "Experimental therapeutic options for clinically localised prostate cancer", the following recommendation on HIFU was made: "If HIFU is offered, the lack of long-term comparative outcome data (>10 y) should be discussed with the patient."

A patient representative, member of the GDG, remarks that an updated prostate cancer guideline was issued on April 16, 2014 in the Netherlands (IKNL) (http://www.oncoline.nl/prostaatcarcinoom). In an introductory note, it stipulates that therapeutic modalities such as cryosurgery, HIFU and focal therapy are out of scope since expertise is limited and long term effectiveness data are lacking. The Dutch GDG "assumes" ("gaat ervan uit") that these therapeutic modalities are used only in the context of a clinical trial after informed consent is obtained from the patients involved.

One stakeholder claims that HIFU should never be used in high risk patients, even not in a trial. The GDG decides not to change the recommendations, given the absence of hard data.

Recommendation

- **Consider HIFU as a treatment option in men with localised prostate cancer only in the context of controlled clinical trials (very low level of evidence; weak recommendation).**

9. HORMONES IN MONO-THERAPY

9.1. Background

In a preparatory phase of this guideline, we conducted a web survey presenting 19 potentially problematic recommendations regarding the management of localised prostate cancer. The target audience for this survey consisted of practitioners involved in prostate cancer care and patients. Surveyed practitioners were urologists, radiotherapists, general practitioners and nurses in urology.[1] One of the presented statements was: “Patients with localised prostate cancer that are not suitable for radical treatment should be treated with hormones”. 41.4% of respondents agreed with this statement. Considering the doubts about the supporting evidence for this, and the obvious lack of consensus among respondents, the GDG decided to produce a *de novo* recommendation on the use of hormones in mono-therapy in localised prostate cancer.

The role of androgen deprivation therapy (medical or surgical castration) has been well established in the treatment of advanced prostate cancer and as an adjunct for men undergoing radiation therapy. It has also been implemented in patients with lesser degrees of prostate cancer, sometimes in mono-therapy. There is ongoing debate about the effectiveness of the latter approach. Moreover, the adverse effects of hormone therapy are substantial, including impotence, decreased libido, hot flashes, and increased fracture risk.

Orchiectomy is a relatively simple procedure with minor surgical risks. It has however fallen out of favour given its psychological impact and possible medical alternatives for androgen deprivation. Medical castration can be accomplished with gonadotropin releasing hormone agonists and antagonists. Leuprolide and goserelin are commonly used gonadotropin releasing hormone agonists and are administered in the form of depot injections or subcutaneous implants. Long-term treatment with gonadotropin releasing hormone agonists supplants the effect of physiologically gonadotropin releasing hormone and is thought to down-regulate its receptors in the pituitary gland, leading to castration levels of testosterone. Androgen receptor antagonists such as flutamide, bicalutamide, and nilutamide represent another class of hormones that are used in patients with prostate cancer. They are used alone or in combination with castration to block the effects of androgens.[171]

9.2. Literature search results

The search of systematic reviews or meta-analysis yielded 1123 hits. Selection by title and abstract resulted in 231 SRs from which 83 were retained on basis of full text. After a quick critical appraisal, no systematic review was of sufficient quality to be considered. The results of this quality appraisal can be found in appendix.

The search of RCTs yielded 3476 hits. Selection by title and abstract and additional hand searching resulted in 103 primary studies from which 56 were retained on basis of full text (Figure 5). Five studies considered adverse events only without discussing efficacy.[172-176] These publications are not considered further in this text, given a total number of 51 RCTs. The list of included and excluded studies can be found in appendix. Observational studies were excluded from our initial search because of their inherent methodological limitations.

Figure 5 – Flowchart of SRs selection on hormone therapy

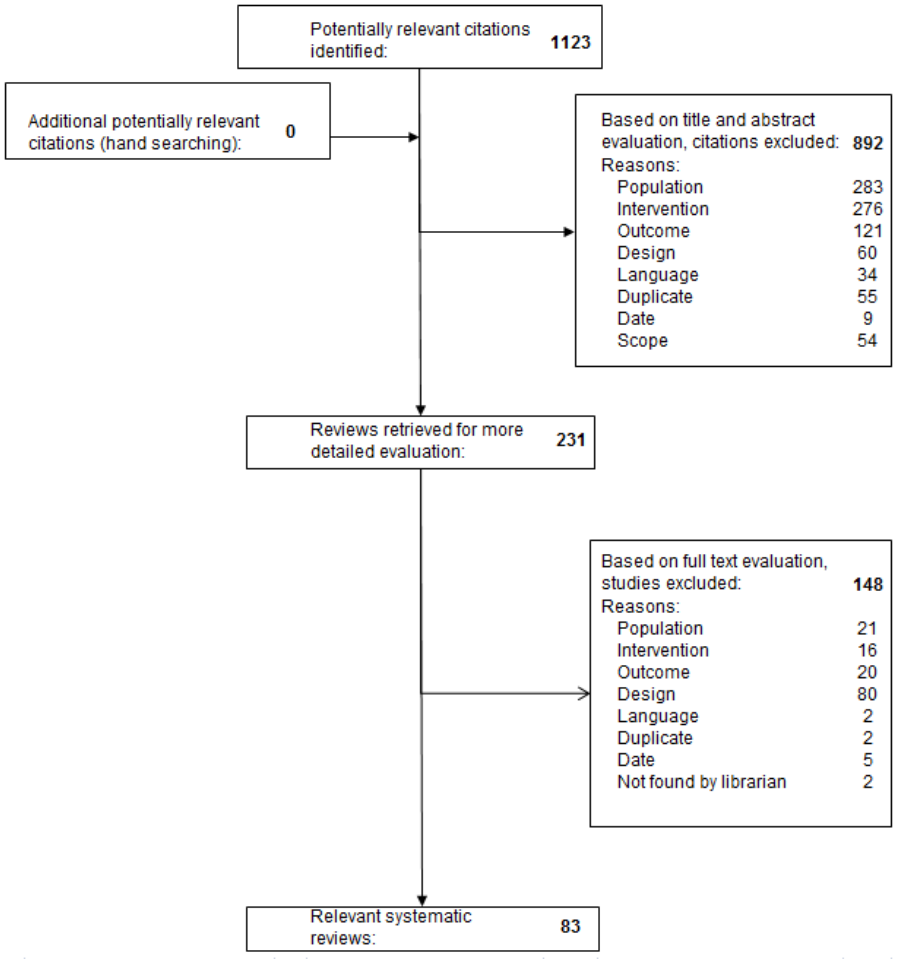
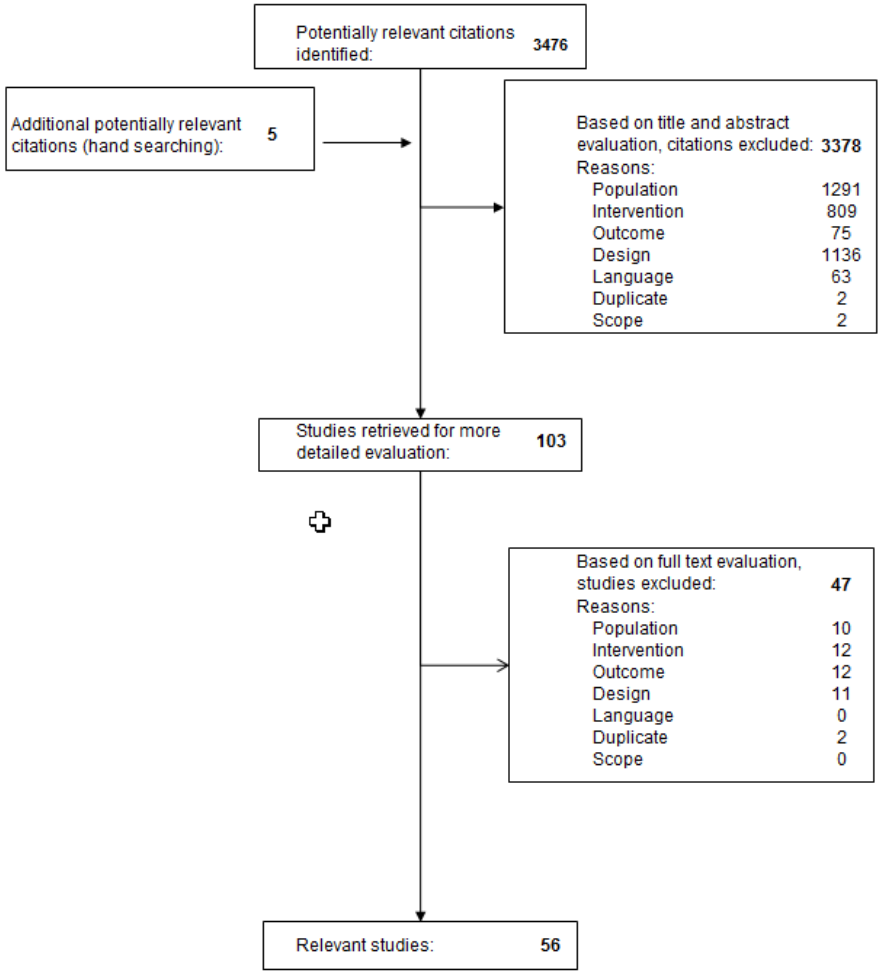


Figure 6 – Flowchart of RCTs selection on hormone therapy



9.2.1. Systematic reviews

Among the eleven systematic reviews selected, none addressed specifically our clinical questions. None of them focused on the efficacy of hormones in mono-therapy in localised PCa. Some reviews considered adverse events of hormone therapy only with no review on efficacy. None of these studies were appropriate to answer our research questions.

9.2.2. Randomised controlled trials

The 51 selected publications (full text publications or abstracts) concerned 10 different trials, some of which belong to one single investigational program. Only one program (EPC), gathering 3 trials, compared hormonal therapy with placebo. We found 8 publications on the EPC program gathering the results of the three RCTs.[105, 177-183] 3 publications on trial 25 (SPCG-6)[184-186] and 3 publications on trial 24.[187-189]

We found 2 different trials on the comparison of immediate versus deferred hormone therapy: EORTC 30891[190-193] and the trial of Lundgren 1995[194]. Five different trials were found on the comparison of different hormone regimens: the trial of Akaza,[195-197] the CS 21 (A) trial,[198-216] the trial of Axcrona,[217, 218] the trial of Anderson[219] and the trial of Lundgren.[194]

Two trials were found on the comparison of hormone versus hormone in addition to another mono-therapy (radiotherapy): NCIC CTG UK PRO7[220-222] and SPCG-7.[223, 224]

Trials studying different dosages of the same hormone were considered not sufficiently relevant to be described further.[225, 226] The quality appraisal of the selected RCTs is provided in appendix. A summary of each trial (even the trials on different dosages) can be found in appendix.

9.3. Evidence supporting the use of hormone-therapy in localised prostate cancer

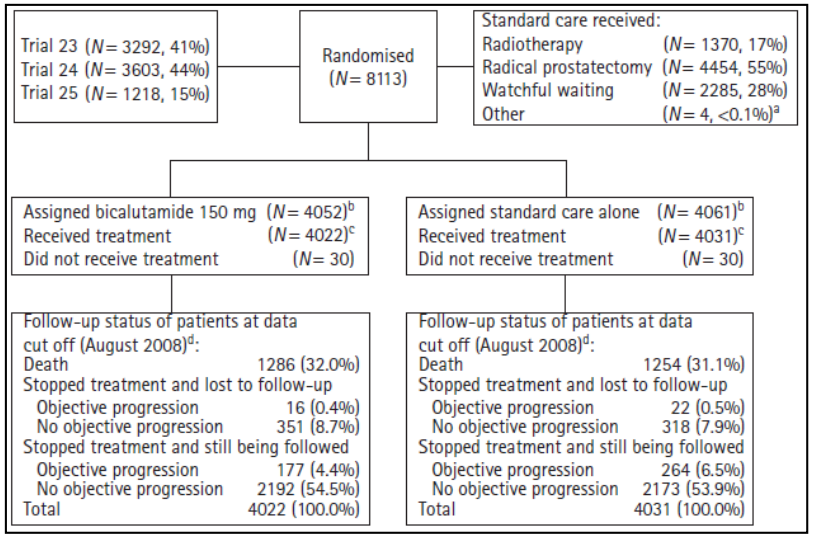
9.3.1. Hormone versus placebo

The “Bicalutamide Early Prostate Cancer (EPC) program” comprised three randomised, double-blind and placebo-controlled trials of an identical design with a low risk of bias: EPC trial 23, 24 and 25.[105, 177-183] Trial 23 was conducted in North America and trial 24 in non-Scandinavian Europe, South Africa, Israel, Mexico and Australia, trial 25 in Scandinavia. Treatment randomisation was conducted separately for each centre. The research question was whether bicalutamide represents a useful treatment option for patients with early prostate cancer, either as adjuvant or in mono-therapy (i.e. in combination with “watchful waiting”). The primary endpoint was “time to objective progression”, indicating the number of days between the date of randomisation and the earliest sign of objective confirmed progression or death of any cause.

Recruitment commenced in August 1995 and was closed in July 1998. A total of 8113 patients were randomised in a 1:1 ratio to receive either bicalutamide 150 mg or matching placebo. The majority of patients had a T1/T2, N0, M0 prostate cancer. The investigational therapy could be given as adjuvant to radical prostatectomy, radiotherapy or watchful waiting. Of the patients recruited in North America (trial 23), 80% had undergone radical prostatectomy, whereas in the Scandinavian study (trial 25), the majority of men (81%) were previously untreated. In trial 24, 65% of men had received treatment of primary curative intent.[177] An overview of the EPC trials is given in Table 13. The level of evidence is based on a critical appraisal of the quality of the evidence (see GRADE profile in Table 14).

The CONSORT diagram displaying the flow of patients through the EPC programmed is shown in Figure 7 and is extracted from Iversen 2010.[183]

Figure 7 – CONSORT diagram of the EPC program



Source: Iversen et al.[183]

Overall, at a median follow-up of 9.7 years, bicalutamide significantly improved progression free survival (PFS) (HR 0.85, 95% CI 0.79–0.91; p=0.001). Compared with placebo there was no difference in overall survival (HR 1.01; 95% CI 0.94-1.09). Patients who derived benefit from bicalutamide in terms of PFS were those with locally advanced disease, with overall survival significantly favouring bicalutamide in patients with locally advanced disease undergoing radiotherapy. Patients with localised disease showed no benefit with bicalutamide when compared with placebo, neither for the risk of objective disease progression (HR 0.85; 95% CI 0.79-0.91; p=0.001) nor for overall survival (no exact HR provided). In the patient subgroup with localised disease and watchful waiting, the risk for objective progression was not significantly altered with bicalutamide (HR 0.93; 95% CI 0.82-1.06: p=0.261) and there was a survival trend in favour of placebo in the (HR 1.15; 95% CI 1.00-1.32; p=0.054).

The EPC trial 25[184-186] enrolled 1218 patients and addressed mainly patients managed with watchful waiting (81%). About 60% of patients had localised disease. The risk of objective progression with bicalutamide versus placebo was 48.3% and 56.3% for all stages. At 7.1 years follow-up, there was no difference in overall mortality (HR 0.91; 95%CI 0.76-1.09: p=0.11). For patients with localised disease, the addition of bicalutamide to standard care resulted in no difference in the reduction of the risk of objective progression (HR 0.85; 95%CI 0.69-1.06; p=015) and in a trend towards decreased overall survival (HR 1.23; 95%CI 0.96-1.58; p=0.11). After a median of 9.7 years follow up, hazard rate for overall survival was 1.24 (1.00-1.54) in patients with watchful waiting.[183] The increased number of deaths in these patients appeared to be due to a number of small imbalances rather than a specific cause. In patients with locally advanced disease, bicalutamide in addition to standard care improved overall survival at 7 years follow-up (HR 0.65; 95% CI 0.50-0.85).[184]

The EPC trial 24[187-189] enrolled 3603 patients, 35% of them were receiving watchful waiting, most often because of severe co-morbidities. In the subgroup of localised cancer, at 7.0 years follow-up results showed that addition of bicalutamide to standard care provided no significant benefit in terms of reduction of the risk of objective progression (HR 0.88; 95% CI 0.76-1.03; p=0.10) or overall survival (no exact HR provided). In the subgroup of locally advanced prostate cancer, addition of bicalutamide to standard care improved reduction of the risk of objective progression (HR 0.66; 95% CI 0.55-0.79; p<0.001) but not overall survival.

Table 13 – Hormone versus placebo

Study	EPC (trials 023, 024, 025)	EPC trial 025 (SPCG-6)	EPC trial 024
Country	Europe, South-Africa, Israel, Mexico, Australia	Norway, Sweden, Denmark, Finland	Non-Scandinavian Europe, South Africa, Israel, Mexico, Australia
Patients n°	8113	1218	3603
Patients age, yr, mean or median	66.9	68.5	68.6
Tumour stage	Non metastatic, T1b-T4, any N	Non metastatic, T1b-T4, any N	Non metastatic, T1b-T4, any N
Hormonal intervention	Bicalutamide 150mg/day (Casodex)	Bicalutamide 150mg/day (Casodex)	Bicalutamide 150mg/day (Casodex)
• **Hormone, class**	Non steroidal antiandrogens	Non steroidal antiandrogens	Non steroidal antiandrogens
• **Hormone, timing**	From 2 weeks of randomization until completion of the treatment period (2 years in trial 023, >5 years in 2 other trials) or until treatment failure.	>5y	>5y
Comparator	Placebo	Placebo	Placebo
Outcome, type	Time to objective disease progression Time to treatment failure Survival Tolerability	PFS OS Adverse events	Disease progression (objectively confirmed PFS) PSA OS Specific mortality Adverse events
Follow-up, mo, median	NA	7.1	5.1

Table 14 – Evidence profile of trials comparing hormone versus placebo in patients with localised PCa

N° of studies/patients	Study design	Methodological quality	Consistency of results	Directness of evidence	Magnitude of effect, %	Other modifying factors	Level of evidence
Outcome: reduction of the risk of objective progression							
1/1218	RCT	Low risk of bias	Only 1 trial	Direct	HR 0.85; 95%CI 0.69-1.06	Publication bias likely	Moderate
Outcome: overall survival at 7 years							
1/1218	RCT	Low risk of bias	Only 1 trial	Direct	HR 1.23; 95%CI 0.96-1.58	Publication bias likely	Moderate
Outcome: overall survival at 9 years (in ptn with watchful waiting)							
1/1218	RCT	Low risk of bias	Only 1 trial	Direct	HR 1.24; 95%CI 1.00-1.54	Publication bias likely	Moderate

9.3.2. Hormone versus hormone

9.3.2.1. Comparing different timing in starting hormone treatment: immediate versus deferred

The EORTC 30891[190-193] compared androgen deprivation therapy (immediate subcapsular orchiectomy or LH-RH analogue Buserelin + initial 2-week cyproterone acetate) with the same treatment deferred until progression. The study enrolled 985 patients, from which about 50% had a T0-T2 stage tumour. All patients either refused or were deemed unsuitable for local curative treatment because the tumour was locally too advanced or because they had short life expectancy and/or severe co-morbidities. At a median follow-up of 12.8y, immediate ADT resulted in a modest but statistically significant increase in overall survival but no significant difference in prostate cancer mortality or symptom free survival. The authors did not provide data on outcomes in patients with localised disease. Therefore, and because of the particularly morbid population this study addressed, we felt that the data originating from this study did not contribute to finding an answer to our research question.

In another study,[194] 285 patients were randomised in 3 groups: one received a combination of polyestradiol phosphate + ethinyloestradiol, one received estramustine phosphate and another deferred endocrine treatment at progression to symptomatic or metastatic disease.[194] The quality appraisal suggested a high risk of bias in this study because of an unclear randomisation procedure and poorly balanced study arms. The results showed no difference in overall survival between the 3 groups although more patients died from prostate cancer in the deferred group (28%) than in the estramutine phosphate (18%) and the polyestradiol phosphate + ethinylestradiol groups (12%). Because of methodological limitations and a low number of events, we felt that the data originating from this study did not contribute to finding an answer to our research question.

An overview of the studies on the different timing in starting hormone treatment is given in Table 15.

Table 15 – Hormone versus hormone: immediate versus deferred

Study	EORTC 30891	Lundgren 1995
Country	Not reported	Sweden
Patients n°	985	285
Patients age, yr, mean or median	73.0	70.0
Tumour stage	T0-TX (mostly T2 and T3)	T0a-T3, NX, M0
Hormonal intervention	Orchiectomy or buserelin (6.3mg suprefact depot) + cyproterone acetate (50mg 3x/day)	Polyestradiol phosphate IM 80 mg every 4 weeks + ethinyloestradiol 50 µg 3X/d (Group A): stop in 1983 because of a high frequency of cardiovascular disease ; instead Polyestradiol phosphate IM 80 mg every 4 weeks alone (Group D) but with only 13 patients and not considered in the calculations. Or Estramustine phosphate 280 mg 2X/d (Group B)
• **Hormone, class**	LHRH agonists + Non steroidal antiandrogens	Oestrogens
• **Hormone, timing**	Immediate	?
Comparator	Deferred orchiectomy or buserelin + cyproterone acetate	Surveillance and deferred endocrine treatment (same as above)
• **Hormone, class**	LHRH agonists + Non steroidal antiandrogens	Oestrogens
• **Hormone, timing**	At disease progression	At progression to symptomatic or metastatic disease
Outcome, type	Overall survival PC mortality Objective progression	Metastases-free survival Cause of death OS Treatment failure
Follow-up, mo, median	12.9y	?

9.3.2.2. Comparing different hormone regimens

In a small (n=78) Japanese study, the LH-RH agonist leuprorelin in mono-therapy (n=73) was compared to leuprorelin in combination with the anti-androgenic agent chlormadinone.[195-197] 65% of participants had localised prostate cancer. Overall survival of participants at 5 years was comparable to the survival of the general Japanese population. Progression free survival at 5 years follow-up was better in the combined treatment group (47% vs 68%). There was no statistically significant difference in all-cause mortality at 10 years follow-up. There was no statistically significant difference in prostate cancer survival at 10 years follow-up. No subgroup analyses were provided.

The CS21 trial is a three armed study comparing different dosages of the gonadotropin releasing hormone antagonist degarelix and the LH-RH agonist leuprolide.[175, 176, 198-209, 211-216] About 30% of patients had localised disease. The primary endpoint of this study was the effect on surrogate endpoints (testosterone and PSA levels). The study was considered not relevant for answering the present clinical questions.

In the Axcrona study,[217, 218] the gonadotropin releasing hormone antagonist degarelix was compared with a combination of the gonadotropin releasing hormone agonist goserelin and bicalutamide.[217, 218] About 30% of patients had localised disease. The primary endpoint was prostate volume reduction after 12 weeks. Prostate volume reduction was achieved to the same degree in both groups. The study was considered not relevant for answering the present clinical question because of it short follow-up time and intermediate endpoint.

In the study of Lundgren 1995[194] (also above-mentioned in 9.3.2.1), the survival rates were compared between a group of patients who received a combination of polyestradiol phosphate and ethinyloestradiol (n=66) and a group of patients who received estramustine phosphate (n=74). No significant difference between both groups were found for metastasis-free survival and overall survival ($p>0.05$). Subgroup-analyses showed an interaction between the cancer grade and the kind of treatment: the combination of polyestradiol phosphate and ethinyloestradiol is correlated with better survival rates in patients with well-differentiated cancer (risk ratio group 1-risk ratio group 2=0.54, $p=0.07$). However in patients with moderately well differentiated tumors the estramustine phosphate seemed to be related to a lower risk of dying or prostate cancer compared to the combination treatment (polyestradiol phosphate and ethinyloestradiol) (risk-ratio group 1-risk ratio group 2=1.93, $p=0.14$). Overall could be stated that no differences were found both groups and that the conclusions of this study may be hampered due to the low number of events and the methodological limitations.

An older study compared estramustine with a combination of polyestradiol plus 17-α-ethinylestradiol.[219] About 45% of 182 patients had a stage II tumour. The primary endpoint was the reduction of the tumour estimated by rectal palpation. No statistical difference was shown between the 2 groups. The study was considered not relevant for answering the present clinical question because it provided no data on hard endpoints.

An overview of the studies on the different hormone regimens is given in Table 16.

Table 16 – Hormone versus hormone: different hormone regimens

Study	Akaza 2006	CS 21 (A)	Axcrona	Anderson 1980	Lundgren 1995
Country	Japan	Not reported	Not reported	Sweden	Sweden
Patients n°	151	610	179	182	285
Patients age, yr, mean or median	76.1, 75.2	73.0	71.9; 73.0	Not reported	70.0
Tumour stage	T1b-T3 + not scheduled for radical prostatectomy	All stages	T1-T4	T2-T4	T0a-T3, NX, M0
Intervention	Leuprorelin acetate depot (3.75mg monthly)	Degarelix (240mg at month 1 than 80mg in G1a or 160mg in G1b)	Degarelix: Starting dose of 240mg Degarelix (40mg/ml, 2x3ml injections)→ on day 28: 80mg Degarelix (20mg/ml, 1x4ml injection)→ on day 56: 80mg Degarelix (20mg/ml, 1x4ml injection)	Estramustine phosphate 840mg/d orally, divided in 2 doses	Polyestradiol phosphate IM 80 mg every 4 weeks + ethinyloestradiol 50 µg 3X/d (Group A): stop in 1983 because of a high frequency of cardiovascular disease ; instead Polyestradiol phosphate IM 80 mg every 4 weeks alone (Group D) but with only 13 patients and not considered in the calculations. Or Estramustine phosphate 280 mg 2X/d (Group B)
• **Hormone, class**	LHRH agonists	LHRH antagonists	LHRH antagonists	Oestrogens	Oestrogens
• **Hormone, timing**	First 2y then change according to physician or patient preference	After 1y re-randomization + follow-up of 3 mo	12wks	24mo	?
Comparator	Leuprorelin acetate depot (3.75mg monthly)	Leuprolide (7.5mg/month)	Goserelin implants (3.6mg) every 28th day + bicalutamide (on day 0: 50mg once-daily oral	Polyestradiol phosphate 80mg IM 1x/mo	Surveillance and deferred endocrine treatment at progression to symptomatic or metastatic disease

	+ chlormadinone acetate (CMA) (100mg/day)		bicalutamide (flare protection) during first 28days)	+ 17-α-ethinylestradiol 2 mg/d for 2 weeks, then 150 µg/d.	
• **Hormone, class**	LHRH agonist + Steroidal progestin	LHRH agonists	LHRH agonists + Non steroidal antiandrogens	Oestrogens	Oestrogens
• **Hormone, timing**					
Outcome, type	PSA levels (recurrence+ response rate) OS Cause-specific survival rate 10y PFS rate	Testosterone level PSA level CV events + mortality PFS rate Time to PSA failure	Testosterone level PSA level IPSS QoL BPH Impact Index Reduction total prostate volume	Tumour regression Adverse events	Metastases-free survival Cause of death OS Treatment failure
Follow-up, mo, median	12wks for response rate, 10y for PFS rate	5y	12 wks	2y	?

9.3.3. Hormone versus hormone + radiotherapy

Two RCTs compared hormone therapy with a combination of hormones and radiotherapy. In the NCIC CTG UK PR07 study,[220-222] the hormonal treatment consists on orchiectomy or LHRH agonist the proportion of localised prostate cancer is very low (13%) and no subgroup analysis was performed according to the stage tumour. This RCT was considered not relevant for answering the present clinical question. In the SPCG-7,[223, 224] treatment with an hormonal combination of leuprorelin and flutamide was compared with the same hormonal treatment plus radiotherapy (70 Gy) started after 3 months. Around 20% of the population sample had a tumour stage <T3 and a stratified by T stage analysis showed a decreased 10-year cumulative incidence of prostate-cancer-specific mortality in the radiotherapy group. In particular, this decrease was evident in patients with T1b–T2 tumours, where the mean absolute risk reduction was 16.0% (95% CI 3.7–28.2). This RCT was considered not relevant for answering the present clinical question.

An overview of the studies on the comparison of hormone therapy versus hormone therapy + radiotherapy, is given in Table 17.

Table 17 – Hormone versus hormone + radiotherapy

Study	NCIC CTG UK PR07	SPCG-7
Country	UK, North America	Norway, Sweden, Denmark
Patients n°	1205	880
Patients age, yr, mean or median	69.7	66
Tumour stage	T3-T4, N0 or NX or M0; T2 with either PSA >40ng/ml or both T2 and PSA >20ng/ml with a Gleason score >8	T1b-T3, N0, M0
Hormonal intervention	Lifelong ADT (choice between bilateral orchiectomy or LHRH agonist (initially given with 2 weeks of anti-androgens which could be continued at investigator's discretion)	Leuprorelin (3.75 mg a month or 11.25 mg every 3 months), for 3 months + simultaneously flutamide 250 mg 3x/d. After 3 mo of total androgen blockade, continued flutamide until progression or death.
• **Hormone, class**	LHRH agonists	LHRH agonists + Non-steroidal antiandrogens
• **Hormone, timing**	See above	See above
Comparator	Same treatment as above and radiotherapy started within 8 weeks of randomization, 4-field box technique The pelvic target volume (45Gy given in 25 fractions over 5 weeks): whole pelvis, prostate, seminal vesicles, external and internal iliac lymph nodes. The prostate target volume (20-24 Gy given in 10-12 fractions over 2-2.5 weeks): prostate gland with known periprostatic tumour extension	After 3 months of the same treatment, patients in the endocrine plus radiotherapy group started radiotherapy (70 Gy).
Outcome, type	Overall survival Disease-specific survival Disease progression Adverse events QoL	Cancer-specific survival PSA recurrence Overall mortality QoL Biopsy result
Follow-up, mo, median	6.0y with maximum of 13.3y	7.6y

9.4. GDG conclusions

The “Early Prostate Cancer (EPC) program” is the only RCT that provides an answer to the question whether hormones in mono-therapy are effective in localised prostate cancer. The results of the Scandinavian study (trial 25) are most relevant for the present clinical question since the hormone therapy was instituted as a mono-therapy in combination with watchful waiting in the majority of patients. In those with localised disease, progression free survival was unaffected by bicalutamide whereas there was a trend for increased overall mortality.

Some RCTs compared different timing, a different regimen of hormonal treatment, or combination of radiotherapy + hormone versus hormone alone. However, the primary endpoint, the shortness of follow-up, the lack of subgroup analysis according to the tumour stage do not allow to consider their results as relevant for answering the present clinical question. Indirectly, various comparisons of hormonal therapies failed to demonstrate any significant effect.

In conclusion, the few data on efficacy found through this literature review, in combination with the substantial known side effects induced by hormone therapy, make this treatment modality currently inappropriate for patients with localised prostate cancer.

9.5. Stakeholders considerations

One patient representative scored a “2” for this recommendation based on a personal experience by a friend. This stakeholder refers to psychological problems in patients who have to deal with active surveillance and cannot cope with the idea that they have cancer. The GDG members explain that in general it appears that the harms induced by hormones are larger than the benefits. It also refers to a previous recommendation “Consider radical treatment with curative intent in men with localised prostate cancer who decline active surveillance”.

It is proposed by stakeholders and accepted by the GDG that the word “hormones” be replaced by “hormonal therapy” since a number of therapeutic agents are no real hormones but drugs that affect the action of hormones by blocking or stimulating their physiological effect.

Recommendation

- **Do not offer hormonal therapy as a unique treatment modality to men with localised prostate cancer (any risk level) (moderate level of evidence; strong recommendation).**

10. IMPLEMENTATION AND UPDATING OF THIS GUIDELINE

10.1. Implementation

10.1.1. Multidisciplinary approach

The need for a multidisciplinary approach is specifically stressed in part-1 of this guideline.[1] The GDG considered it vital to remind the user of the present guideline of the importance of this recommendation. Therefore it is repeated in the text that, before any treatment decision can be made, an assessment of a man's overall health status, his individual life expectancy and co-morbidities has to be undertaken during a multidisciplinary team meeting.

10.1.2. Patient-centred care

Several recommendations that are formulated in this guideline stress the need to include a patient's (and if he wish his partner's) preferences in therapeutic decision making. The recommendations not only consider beneficial aspects but also potential adverse effects of treatment.

It was beyond the scope of the present guideline to perform a search and an assessment of tools that are intended to assist a patient (and his partner) in deciding which of the proposed therapeutic option to choose.

10.1.3. Barriers and facilitators for implementation of this guideline

The identification of potential barriers and facilitators related to the use of this guideline was limited to a discussion held during the stakeholders meeting. More sophisticated methods could be used, but this would go beyond the scope of this project. More information on the identification of barriers and facilitators in guidelines implementation can be found in a recent KCE-report.[227]

A possible barrier for implementation could be that the guideline is not sufficiently known by the health care professionals involved in prostate cancer care. Stakeholders stressed the importance of wide dissemination of the guideline through several websites and the professional societies.

During the stakeholders meeting, the algorithm (flowchart) proposed by the GDG was considered as very useful. Some changes in its lay-out were proposed and executed. The publication of the guideline on EBMPracticeNet's platform was critically acclaimed because it can be expected to facilitate the use in clinical practice by providing assistance at the point of care. A potential barrier according to some stakeholders could be the fact that some potential users might consider such a guideline (in general) as outdated immediately after its publication, given the large amount of time between the literature search for evidence and the publication of the guideline.

10.1.4. Actors of the implementation of this guideline

Clinical guidelines provide a tool for physicians to consult at different stages of the patient management pathway: screening, diagnosis, treatment and follow-up. They are developed according to highly codified principles, based on scientific information regularly updated from the international literature. KCE formulates recommendations addressed to specific audiences (clinicians, decision-makers, sickness funds, NIHDI, professional organizations, hospital managers). KCE is not involved in the decision making process itself, or in the execution of the decisions.

The implementation of this guideline will be facilitated/conducted by the "College of Oncology". An online implementation tool similar to the tools accompanying previous guidelines will be developed (www.collegeoncologie.be).

A summary of the guideline will also become accessible on www.ebmpracticenet.be, a Belgian database of evidence-based practice guidelines. It is sponsored by the NIHDI and is free for use by Belgian practitioners. Moreover, the software that is incorporated in the electronic medical record (EMR) system of Belgian general practitioners enables a direct connection of a patient's EMR with the database, further promoting the implementation of the guideline(s).

Furthermore, the content of this guideline is intended to be disseminated by scientific and professional organisations. They can produce attractive and user-friendly tools tailored to caregivers groups. They will also play a key role by a dissemination that makes use of diverse channels such as websites or sessions of continuing medical education.

10.2. Monitoring quality of care

This guideline should be considered as a starting point to develop quality improvement programs that targets all caregivers concerned. It can be used as a tool to support health policies to improve the quality of care, e.g. through the support of actions to increase caregivers' awareness and to improve their practice, or through the development (or revision) of sets of process and outcome quality indicators.

A series of performance quality indicators have for example been proposed by the Scottish Cancer Taskforce.[228] They include e.g. the percentage of patients with stage pT2 prostate cancer who underwent radical prostatectomy and in whom cancer is present at the margin. A target of <25% is proposed for this quality indicator.

KCE previously recommended to set up an integrative quality system in oncology, covering the development and implementation of clinical practice guidelines, the monitoring of the quality of care with quality indicators, feedback to health care providers and organizations and targeted actions to improve the quality if needed.[229]

10.3. Guideline update

In view of the rapidly evolving evidence, this guideline should be updated every 5 years. If, in the meantime, important new evidence would become available, this should be taken into consideration.

The KCE processes foresee that the relevance of an update would be yearly assessed for each published guideline by the authors. Decisions are made on the basis of new scientific publications on a specific topic (e.g. Cochrane reviews, RCTs on medications or interventions). Potential interest for groups of health practitioners is also considered in this process.

This appraisal leads to a decision on whether to update or not a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

REFERENCES

1. Mambourg F, Jonckheer P, Piérart J, Van Brabandt H. A national clinical practice guideline on the management of localised prostate cancer. Brussels: Belgian Health Care Knowledge Centre (KCE); 2012.
2. Jonckheer P, Van Landeghem S, Christiaens W, De Winter L, Piérart J, Mertens R. The decisional process for the choice of active surveillance in localised prostate cancer. Brussel: 2013.
3. Gandaglia G, Sammon JD, Chang SL, Choueiri TK, Hu JC, Karakiewicz PI, et al. Comparative Effectiveness of Robot-Assisted and Open Radical Prostatectomy in the Postdissemination Era. J Clin Oncol. 2014.
4. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol. 2011;59(1):61-71.
5. Fervers B, Burgers JS, Haugh MC, Latreille J, Mlika-Cabanne N, Paquet L, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. Int J Qual Health Care. 2006;18(3):167-76.
6. Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol. 2008;19(3):420-32.
7. Abdel-Wahab M, Mahmoud O, Merrick G, Hsu IC, Arterbery VE, Ciezki JP, et al. ACR Appropriateness Criteria(R) external-beam radiation therapy treatment planning for clinically localized prostate cancer. J Am Coll Radiol. 2012;9(4):233-8.
8. American College of Radiology (ACR), American Society for Radiation Oncology (ASTRO). ACR–ASTRO practice guideline for transperineal permanent brachytherapy of prostate cancer. Reston (VA): Agency for Healthcare Research and Quality (AHRQ); 2010. 2/13/2013. Available from: http://guideline.gov/content.aspx?id=32531
9. American Urological Association Education and Research Inc. Best practice policy statement on cryosurgery for the treatment of

localized prostate cancer. Linthicum (MD): 2008. 2/13/2013. Available from: http://guideline.gov/content.aspx?id=13162

10. Arranz Arija JA, Cassinello Espinosa J, Climent Duran MA, Rivero Herrero F, Seom. SEOM clinical guidelines for treatment of prostate cancer. Clin Transl Oncol. 2012;14(7):520-7.
11. Aus G, Abbou CC, Bolla M, Heidenreich A, Schmid HP, van Poppel H, et al. EAU guidelines on prostate cancer. Eur Urol. 2005;48(4):546-51.
12. Babaian RJ, Donnelly B, Bahn D, Baust JG, Dineen M, Ellis D, et al. Best practice statement on cryosurgery for the treatment of localized prostate cancer. J Urol. 2008;180(5):1993-2004.
13. Bauman G, Rumble RB, Chen J, Loblaw A, Warde P, Panel amotIIE. The Role of IMRT in Prostate Cancer. 2010. Available from: http://www.cancercare.on.ca
14. Bohmer D, Wenz F, Martin T, Sedlmayr F, Hinkelbein W, Wiegel T. [Radiation therapy for prostate cancer in the new S3 guideline. Part 1: localized and locally advanced prostate cancer]. Urologe A. 2010;49(2):211-5.
15. Casas F, Borras JM, Ferrer F, Guanyabens N, Gutierrez del Pozo R, Leon C, et al. Evidence-based consensus recommendations to improve the quality of life in prostate cancer treatment. Clin Transl Oncol. 2010;12(5):346-55.
16. de Reijke TM, Battermann JJ, van Moorselaar RJ, de Jong IJ, Visser AP, Burgers JS. Richtlijn 'Prostaatcarcinoom: diagnostiek en behandeling'. Ned Tijdschr Geneeskd. 2008;152(32):1771-5.
17. Droz JP, Balducci L, Bolla M, Emberton M, Fitzpatrick JM, Joniau S, et al. Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology. BJU Int. 2010;106(4):462-9.
18. Elliott S, Latini DM, Walker LM, Wassersug R, Robinson JW, Group ADTSW. Androgen deprivation therapy for prostate cancer: recommendations to improve patient and partner quality of life. J Sex Med. 2010;7(9):2996-3010.
19. Frank S, Arterbery V, Merrick G, Hsu I, Abdel-Wahab M, Ciezki J, et al. ACR Appropriateness Criteria® permanent source brachytherapy for prostate cancer. Reston (VA): Agency for Healthcare Research and Quality (AHRQ); 2010. Available from: http://guideline.gov/content.aspx?id=32605
20. Expert Panel on Radiation Oncology-Prostate, Frank SJ, Arterbery VE, Hsu IC, Abdel-Wahab M, Ciezki JP, et al. American College of Radiology Appropriateness Criteria permanent source brachytherapy for prostate cancer. Brachytherapy. 2011;10(5):357-62.
21. Gans W. Re: Best practice statement on cryosurgery for the treatment of localized prostate cancer R. J. Babaian, B. Donnelly, D. Bahn, J. G. Baust, M. Dineen, D. Ellis, A. Katz, L. Pisters, D. Rukstalis, K. Shinohara and J. B. Thrasher J Urol 2008; 180: 1993-2004. J Urol. 2009;181(5):2388.
22. Grimm MO, Thomas C, Frohner M, Wiegel T, Heidenreich A, Thuroff JW, et al. [Pelvic lymphadenectomy and radical prostatectomy. Recommendations of the German S3 guideline]. Urologe A. 2010;49(2):206-10.
23. HAS. High Intensity Focalized Ultrasound for the treatment of localized prostate cancer. 2010. Available from: http ://www.has-sante.fr
24. HAS. Cancer de la prostate. Guide - affection de longue duree. 2012. Available from: www.has-sante.fr
25. Hassen WA, Karsan FA, Abbas F, Beduk Y, El-Khodary A, Ghosn M, et al. Modification and implementation of NCCN guidelines on prostate cancer in the Middle East and North Africa region. Journal of the National Comprehensive Cancer Network. 2010;8(3).
26. Hatiboglu G, Teber D, Hohenfellner M. Robot-assisted prostatectomy: the new standard of care. Langenbecks Arch Surg. 2012;397(3):343-52.
27. Hayden AJ, Martin JM, Kneebone AB, Lehman M, Wiltshire KL, Skala M, et al. Australian & New Zealand Faculty of Radiation Oncology Genito-Urinary Group: 2010 consensus guidelines for definitive external beam radiotherapy for prostate carcinoma. J Med Imaging Radiat Oncol. 2010;54(6):513-25.

28. Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP, et al. EAU guidelines on prostate cancer. Eur Urol. 2008;53(1):68-80.
29. Horwich A, Parker C, Bangma C, Kataja V, Esmo Guidelines Working Group. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2010;129(21).
30. Horwich A, Hugosson J, de Reijke T, Wiegel T, Fizazi K, Kataja V, et al. Prostate cancer: ESMO Consensus Conference Guidelines 2012. Ann Oncol. 2013;24(5):1141-62.
31. Kamidono S, Ohshima S, Hirao Y, Suzuki K, Arai Y, Fujimoto H, et al. Evidence-based clinical practice Guidelines for Prostate Cancer (Summary - JUA 2006 Edition). Int J Urol. 2008;15(1):1-18.
32. Kovacs G, Potter R, Loch T, Hammer J, Kolkman-Deurloo IK, de la Rosette JJ, et al. GEC/ESTRO-EAU recommendations on temporary brachytherapy using stepping sources for localised prostate cancer. Radiother Oncol. 2005;74(2):137-48.
33. Kuykendal AR, Hendrix LH, Salloum RG, Godley PA, Chen RC. Guideline-discordant androgen deprivation therapy in localized prostate cancer: patterns of use in the medicare population and cost implications. Ann Oncol. 2013;24(5):1338-43.
34. Langley S, Ahmed HU, Al-Qaisieh B, Bostwick D, Dickinson L, Veiga FG, et al. Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer. BJU International. 2012;1:7-16.
35. Lukka H, Waldron T, Chin J, Mayhew L, Warde P, Winquist E, et al. High-intensity focused ultrasound for prostate cancer: a practice guideline. Can Urol Assoc J. 2010;4(4):232-6.
36. Maceira Rozas Mdel C, Rey Liste T, Garcia Caeiro AL, Garcia Comesana J. Recommendations for treatment with IMRT for prostate and head-neck cancer. Axencia de Avaliacion de Tecnoloxias Sanitarias de Galicia. Clin Transl Oncol. 2006;8(4):262-5.
37. Mohler JL, Armstrong AJ, Bahnson RR, Boston B, Busby JE, D'Amico AV, et al. Prostate cancer, Version 3.2012: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2012;10(9):1081-7.
38. Montorsi F, Wilson TG, Rosen RC, Ahlering TE, Artibani W, Carroll PR, et al. Best practices in robot-assisted radical prostatectomy: recommendations of the Pasadena Consensus Panel. Eur Urol. 2012;62(3):368-81.
39. Moran BJ DP, Merrick G, Hsu IC, Abdel-Wahab M, Arterbery VE, Ciezki JP, Frank SJ, Mohler JL, Rosenthal SA, Rossi CJ Jr, Yamada Y, Expert Panel on Radiation Oncology-Prostate. ACR Appropriateness Criteria® definitive external beam irradiation in stage T1 and T2 prostate cancer. Reston (VA): 2010. Available from: http://guideline.gov/content.aspx?id=32635
40. Moran BJ, DeRose P, Hsu IC, Abdel-Wahab M, Arterbery VE, Ciezki JP, et al. ACR Appropriateness Criteria(R) definitive external beam irradiation in stage T1 and T2 prostate cancer. Am J Clin Oncol. 2011;34(6):636-47.
41. NICE. Low dose rate brachytherapy for localised prostate cancer. London (UK): 2005. Interventional Procedure Guidance 132 (1-84629-059-7). Available from: http://www.nice.org.uk/nicemedia/live/11150/31307/31307.pdf
42. NICE. High-intensity focused ultrasound for prostate cancer. London (UK): National Institute for Health and Clinical Excellence; 2005. Interventional Procedure Guidance 118
43. NICE. Cryotherapy as a primary treatment for prostate cancer. London (UK): National Institute for Health and Clinical Excellence; 2005. Interventional Procedure Guidance 145
44. NICE. Laparoscopic radical prostatectomy. London (UK): National Institute for Health and Clinical Excellence; 2006. Interventional procedure guidance 193
45. NICE. High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. London (UK): National Institute for Health and Clinical Excellence; 2006. Interventional Procedure Guidance 174
46. NICE. Denosumab for the treatment of therapy induced bone loss in nonmetastatic prostate cancer (terminated appraisal). London (UK):

2010. NICE technology appraisal 194 (978-1-84936-316-7). Available from: http://www.nice.org.uk/nicemedia/live/13059/49898/49898.pdf

47. NICE. Review of Clinical Guideline (CG58), Prostate cancer: diagnosis and treatment. London (UK): National Institute for Health and Clinical Excellence; 2011.
48. NICE. Focal therapy using high-intensity focused ultrasound for localised prostate cancer. London (UK): National Institute for Health and Clinical Excellence; 2012. NICE interventional procedure guidance. guidance.nice.org.uk/ipg424
49. NICE. Focal therapy using cryoablation for localised prostate cancer. London (UK): National Institute for Health and Clinical Excellence; 2012. NICE interventional procedure guidance. 423guidance.nice.org.uk/ipg423
50. NICE NCCfC. Prostate cancer. Diagnosis and treatment. CG58. London (UK): 2008. NICE clinical guideline 58. Available from: http://guideline.gov/content.aspx?id=14315
51. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer [Web page].2011. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
52. Prostate Cancer Clinical Guideline Update Panel. Guideline for the management of clinically localized prostate cancer 2007 update. Linthicum (MD): American Urological Association Education and Research, Inc.; 2007. Available from: http://guideline.gov/content.aspx?id=11446
53. Roach Mr, Hanks G, Thames H, Jr., Schellhammer P, Shipley WU, Sokol GH, 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(4):965-74.
54. Rosenthal SA, Bittner NH, Beyer DC, Demanes DJ, Goldsmith BJ, Horwitz EM, et al. American Society for Radiation Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the transperineal permanent brachytherapy of prostate cancer. Int J Radiat Oncol Biol Phys. 2011;79(2):335-41.
55. Saad F, Higano CS, Sartor O, Colombel M, Murray R, Mason MD, et al. The role of bisphosphonates in the treatment of prostate cancer: recommendations from an expert panel. Clin Genitourin Cancer. 2006;4(4):257-62.
56. Salomon L, Azria D, Bastide C, Beuzeboc P, Cormier L, Cornud F, et al. Recommandations en Onco-Urologie 2010: Cancer de la prostate. Progres en Urologie. 2010;20(4).
57. Sidhom MA, Kneebone AB, Lehman M, Wiltshire KL, Millar JL, Mukherjee RK, et al. Post-prostatectomy radiation therapy: consensus guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group. Radiother Oncol. 2008;88(1):10-9.
58. Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagino ED, Cookson MS, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol. 2007;177(6):2106-31.
59. Working Group of the Clinical Practice Guideline on Prostate Cancer Treatment. Clinical practice guideline for prostate cancer treatment Madrid: Aragon Institute of Health Sciences.; 2008. Clinical practice guidelines in the NHS I+CS 2006/02. Available from: http://guideline.gov/content.aspx?id=16311
60. Weissbach L, Schaefer C, Heidenreich A. [A paradigm shift. Defensive strategies for the treatment of localized prostate cancer in the new S3 guideline]. Urologe A. 2010;49(2):199-205.
61. Wolff JM, Mason M. Drivers for change in the management of prostate cancer - guidelines and new treatment techniques. BJU International. 2012;6:33-41.
62. Yamada Y, Rogers L, Demanes DJ, Morton G, Prestidge BR, Pouliot J, et al. American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. Brachytherapy. 2012;11(1):20-32.
63. Zumsteg ZS, Zelefsky MJ. Short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer undergoing dose-escalated radiotherapy: the standard of care? Lancet Oncol. 2012;13(6):e259-69.
64. Oncoline. Prostate cancer. Vereniging integrale kankercentra; 2007.

65. NICE. The guidelines manual 2009. 2009. Available from: http://www.nice.org.uk/media/615/64/The_guidelines_manual_2009.pdf
66. NICE NCCfC. Prostate cancer: diagnosis and treatment. Clinical Guideline. Full Guideline. Draft for consultation. (480 pages). London (UK): 2014. NICE Clinical Guidelines. Available from: http://www.nice.org.uk/nicemedia/live/14348/66232/66232.pdf
67. NICE NCCfC. Prostate cancer: diagnosis and treatment. Draft for consultation. (49 pages) 2013. NICE Clinical Guidelines. Available from: http://www.nice.org.uk/nicemedia/live/13583/64486/64486.pdf
68. NICE NCCfC. Prostate cancer: diagnosis and treatment. Clinical Guideline. Full Guideline. Draft for consultation. (453 pages). London (UK): 2013. NICE Clinical Guidelines. Available from: http://www.nice.org.uk/nicemedia/live/13583/64485/64485.pdf
69. NICE NCCfC. Prostate cancer: diagnosis and treatment. Update of clinical guideline 58. Evidence review. Draft for consultation. (1353 pages). 2013. NICE Clinical Guidelines. Available from: http://www.nice.org.uk/nicemedia/live/13583/64489/64489.pdf
70. NICE. Prostate cancer: diagnosis and treatment. CG 175. (46 pages). 2014. NICE clinical guidelines (NICE clinical guideline 175). Available from: http://www.nice.org.uk/nicemedia/live/14348/66226/66226.pdf
71. Obyn C, Mambourg F. Rapid assessment of a selection of new treatments for prostate cancer and benign prostate hypertrophy. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2008 24/10/2008. KCE Reports 89. Available from: https://kce.fgov.be/publication/report/rapid-assessment-of-a-selection-of-new-treatments-for-prostate-cancer-and-benign-
72. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20.
73. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
74. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol. 2013;66(2):151-7.
75. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719-25.
76. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. Chest. 2006;129(1):174-81.
77. Schunemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med. 2006;174(5):605-14.
78. Dubbelman YD, Dohle GR, Schroder FH. Sexual function before and after radical retropubic prostatectomy: A systematic review of prognostic indicators for a successful outcome. Eur Urol. 2006;50(4):711-8; discussion 8-20.
79. Matthew AG, Goldman A, Trachtenberg J, Robinson J, Horsburgh S, Currie K, et al. Sexual dysfunction after radical prostatectomy: prevalence, treatments, restricted use of treatments and distress. J Urol. 2005;174(6):2105-10.
80. Perez MA, Meyerowitz BE, Lieskovsky G, Skinner DG, Reynolds B, Skinner EC. Quality of life and sexuality following radical prostatectomy in patients with prostate cancer who use or do not use erectile aids. Urology. 1997;50(5):740-6.
81. Nam RK, Cheung P, Herschorn S, Saskin R, Su J, Klotz LH, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. Lancet Oncol. 2014;15(2):223-31.
82. Boorjian SA, Eastham JA, Graefen M, Guillonneau B, Karnes RJ, Moul JW, et al. A critical analysis of the long-term impact of radical

prostatectomy on cancer control and function outcomes. Eur Urol. 2012;61(4):664-75.

83. Rapiti E, Fioretta G, Verkooijen HM, Zanetti R, Schmidlin F, Shubert H, et al. Increased risk of colon cancer after external radiation therapy for prostate cancer. Int J Cancer. 2008;123(5):1141-5.
84. Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2005;352(19):1977-84.
85. Steineck G, Helgesen F, Adolfsson J, Dickman PW, Johansson JE, Norlen BJ, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med. 2002;347(11):790-6.
86. Akakura K, Suzuki H, Ichikawa T, Fujimoto H, Maeda O, Usami M, et al. A randomized trial comparing radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy for locally advanced prostate cancer: results at median follow-up of 102 months. Jpn J Clin Oncol. 2006;36(12):789-93.
87. Paulson DF, Lin GH, Hinshaw W, Stephani S. Radical surgery versus radiotherapy for adenocarcinoma of the prostate. J Urol. 1982;128(3):502-4.
88. Nilsson S, Norlen BJ, Widmark A. A systematic overview of radiation therapy effects in prostate cancer. Acta Oncol. 2004;43(4):316-81.
89. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367(3):203-13.
90. Wolanski P, Chabert C, Jones L, Mullavey T, Walsh S, Gianduzzo T. Preliminary results of robot-assisted laparoscopic radical prostatectomy (RALP) after fellowship training and experience in laparoscopic radical prostatectomy (LRP). BJU Int. 2012;110 Suppl 4:64-70.
91. Magheli A, Gonzalgo ML, Su LM, Guzzo TJ, Netto G, Humphreys EB, et al. Impact of surgical technique (open vs laparoscopic vs robotic-assisted) on pathological and biochemical outcomes following radical prostatectomy: an analysis using propensity score matching. BJU Int. 2011;107(12):1956-62.
92. Drouin SJ, Vaessen C, Hupertan V, Comperat E, Misrai V, Haertig A, et al. Comparison of mid-term carcinologic control obtained after open, laparoscopic, and robot-assisted radical prostatectomy for localized prostate cancer. World J Urol. 2009;27(5):599-605.
93. Ramsay C. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health Technology Assessment. 2012;16(41).
94. Fiori. Pure versus robot-assisted laparoscopic prostatectomy: Single centre, single surgeon ex-perience. In: Proceedings of; 2012: Journal of Urology.
95. Asimakopoulos AD, Pereira Fraga CT, Annino F, Pasqualetti P, Calado AA, Mugnier C. Randomized comparison between laparoscopic and robot-assisted nerve-sparing radical prostatectomy. J Sex Med. 2011;8(5):1503-12.
96. Mirza M, Art K, Wineland L, Tawfik O, Thrasher JB. A comparison of radical perineal, radical retropubic, and robot-assisted laparoscopic prostatectomies in a single surgeon series. Prostate Cancer. 2011;2011:878323.
97. Tewari A, Srivasatava A, Menon M. A prospective comparison of radical retropubic and robot-assisted prostatectomy: experience in one institution. BJU Int. 2003;92(3):205-10.
98. Ball AJ, Gambill B, Fabrizio MD, Davis JW, Given RW, Lynch DF, et al. Prospective longitudinal comparative study of early health-related quality-of-life outcomes in patients undergoing surgical treatment for localized prostate cancer: a short-term evaluation of five approaches from a single institution. J Endourol. 2006;20(10):723-31.
99. Malcolm JB, Fabrizio MD, Barone BB, Given RW, Lance RS, Lynch DF, et al. Quality of life after open or robotic prostatectomy, cryoablation or brachytherapy for localized prostate cancer. J Urol. 2010;183(5):1822-8.
100. Miller J, Smith A, Kouba E, Wallen E, Pruthi RS. Prospective evaluation of short-term impact and recovery of health related quality of life in men undergoing robotic assisted laparoscopic

radical prostatectomy versus open radical prostatectomy. J Urol. 2007;178(3 Pt 1):854-8; discussion 9.

101. Berge V, Berg RE, Hoff JR, Wessel N, Diep LM, Karlsen SJ, et al. A prospective study of transition from laparoscopic to robot-assisted radical prostatectomy: quality of life outcomes after 36-month follow-up. Urology. 2013;81(4):781-6.
102. Willis DL, Gonzalgo ML, Brotzman M, Feng Z, Trock B, Su LM. Comparison of outcomes between pure laparoscopic vs robot-assisted laparoscopic radical prostatectomy: a study of comparative effectiveness based upon validated quality of life outcomes. BJU Int. 2012;109(6):898-905.
103. Camberlin C, Senn A, Leys M, De Laet C. Robot assisted surgery. A Health Technology Assessment. Brussels: 2009. KCE reports 104C. Available from: https://kce.fgov.be/sites/default/files/page_documents/d20091027309.pdf
104. Van Thielen R, Neirynck C. De kostprijs van prostaatchirurgie in Belgie in 2010. Brussels: Onafhankelijke Ziekenfondsen; 2012. Available from: http://www.mloz.be/files/prostatenl03-04-2012b.pdf
105. McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU Int. 2006;97(2):247-54.
106. Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med. 1999;341(24):1781-8.
107. Wirth. Hormonal therapy for locally advanced prostate. In: Proceedings of International Journal of Urology; 2012.
108. Kumar S, Shelley M, Harrison C, Coles B, Wilt TJ, Mason MD. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. Cochrane Database Syst Rev. 2006(4):CD006019.
109. Dearnaley DP, Hall E, Lawrence D, Huddart RA, Eeles R, Nutting CM, et al. Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. Br J Cancer. 2005;92(3):488-98.
110. Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol. 2007;8(6):475-87.
111. Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, 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;24(13):1990-6.
112. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys. 2002;53(5):1097-105.
113. Yeoh EE, Fraser RJ, McGowan RE, Botten RJ, Di Matteo AC, Roos DE, et al. Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: early results of a Phase III randomized trial. Int J Radiat Oncol Biol Phys. 2003;55(4):943-55.
114. Lukka H, Hayter C, Julian JA, Warde P, Morris WJ, Gospodarowicz M, et al. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. J Clin Oncol. 2005;23(25):6132-8.
115. Norderhaug I, Dahl O, Hoisaeter PA, Heikkila R, Klepp O, Olsen DR, et al. Brachytherapy for prostate cancer: a systematic review of clinical and cost effectiveness. Eur Urol. 2003;44(1):40-6.
116. Doust J, Miller E, Duchesne G, Kitchener M, Weller D. A systematic review of brachytherapy. Is it an effective and safe treatment for localised prostate cancer? Aust Fam Physician. 2004;33(7):525-9.
117. Hummel S, Paisley S, Morgan A, Currie E, Brewer N. Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review. Health Technol Assess. 2003;7(33):iii, ix-x, 1-157.

118. Pollack A, Walker G, Horwitz EM, Price R, Feigenberg S, Konski AA, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. J Clin Oncol. 2013;31(31):3860-8.
119. Van den Steen D, Hulstaert F, Camberlin C. Intensity-modulated radiotherapy (IMRT). Brussels: Belgian Health Care Knowledge Centre (KCE); 2007. D2007/10.273/34Health Technology Assessment (HTA) Available from: https://kce.fgov.be/sites/default/files/page_documents/d20071027334.pdf
120. Lee WR. Prostate cancer and the hypofractionation hypothesis. J Clin Oncol. 2013;31(31):3849-51.
121. Pieters BR, de Back DZ, Koning CC, Zwinderman AH. Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: a systematic review. Radiother Oncol. 2009;93(2):168-73.
122. Bannuru RR, Dvorak T, Obadan N, Yu WW, Patel K, Chung M, et al. Comparative evaluation of radiation treatments for clinically localized prostate cancer: an updated systematic review. Ann Intern Med. 2011;155(3):171-8.
123. Wong WW, Vora SA, Schild SE, Ezzell GA, Andrews PE, Ferrigni RG, et al. Radiation dose escalation for localized prostate cancer: intensity-modulated radiotherapy versus permanent transperineal brachytherapy. Cancer. 2009;115(23):5596-606.
124. da Silva Franca CA, Vieira SL, Carvalho AC, Bernabe AJ, Penna AB. Localized prostate cancer with intermediate- or high-risk features treated with combined external beam radiotherapy and iodine-125 seed brachytherapy. Brachytherapy. 2010;9(4):307-12.
125. Merrick GS, Wallner KE, Butler WM, Galbreath RW, Taira AV, Orio P, et al. 20 Gy versus 44 Gy of supplemental external beam radiotherapy with palladium-103 for patients with greater risk disease: results of a prospective randomized trial. Int J Radiat Oncol Biol Phys. 2012;82(3):e449-55.
126. Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. 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;84(2):114-20.
127. Hoskin PJ, Rojas AM, Ostler PJ, Hughes R, Lowe GJ, Bryant L. Quality of life after radical radiotherapy for prostate cancer: longitudinal study from a randomised trial of external beam radiotherapy alone or in combination with high dose rate brachytherapy. Clin Oncol (R Coll Radiol). 2013;25(5):321-7.
128. Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet. 2005;366(9485):572-8.
129. Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, Brereton HD, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol. 2008;26(15):2497-504.
130. Denham JW, Steigler A, Lamb DS, Joseph D, Turner S, Matthews J, 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;12(5):451-9.
131. Denham JW, Wilcox C, Joseph D, Spry NA, Lamb DS, Tai KH, et al. Quality of life in men with locally advanced prostate cancer treated with leuprorelin and radiotherapy with or without zoledronic acid (TROG 03.04 RADAR): secondary endpoints from a randomised phase 3 factorial trial. Lancet Oncol. 2012;13(12):1260-70.
132. Denham JW, Wilcox C, Lamb DS, Spry NA, Duchesne G, Atkinson C, et al. Rectal and urinary dysfunction in the TROG 03.04 RADAR trial for locally advanced prostate cancer. Radiother Oncol. 2012;105(2):184-92.
133. Robertson CN, Sliwinski A, Delisio J, Wallen E, Ward JF, Orovan W, et al. Morbidity of high intensity focused ultrasound (HIFU) as a primary monotherapy for low-risk localized prostate cancer: Outcomes from the ENLIGHT trial. Urology. 2011;78(3):S25-S6.
134. Blana A, Robertson CN, Brown SC, Chaussy C, Crouzet S, Gelet A, et al. Complete high-intensity focused ultrasound in prostate cancer: outcome from the @-Registry. Prostate Cancer Prostatic Dis. 2012;15(3):256-9.

135. Anonymous. Management of localised prostate cancer: watchful waiting, surgery or radiation therapy, depending on the natural course, which is often relatively slow. Prescrire Int. 2012;21(131):242-8.
136. Ahmed HU, Emberton M. Active surveillance and radical therapy in prostate cancer: can focal therapy offer the middle way? World J Urol. 2008;26(5):457-67.
137. Cordeiro ER, Cathelineau X, Thuroff S, Marberger M, Crouzet S, de la Rosette JJ. High-intensity focused ultrasound (HIFU) for definitive treatment of prostate cancer. BJU Int. 2012;110(9):1228-42.
138. Iberti CT, Mohamed N, Palese MA. A review of focal therapy techniques in prostate cancer: clinical results for high-intensity focused ultrasound and focal cryoablation. Rev. urol. 2011;13(4):e196-202.
139. Lukka H, Waldron T, Chin J, Mayhew L, Warde P, Winquist E, et al. High-intensity Focused Ultrasound for Prostate Cancer: A Systematic Review. Clinical Oncology. 2011;23(2):117-27.
140. Ranjan P, Saurabh G, Bansal R, Gupta A. High intensity focused ultrasound vs. cryotherapy as primary treatment for prostate cancer. INDIAN J. UROL. 2008;24(1):16-21.
141. Rebillard X, Soulie M, Chartier-Kastler E, Davin JL, Mignard JP, Moreau JL, et al. High-intensity focused ultrasound in prostate cancer; a systematic literature review of the French Association of Urology. BJU International. 2008;101(10):1205-13.
142. Tsakiris P, Thuroff S, De La Rosette J, Chaussy C. Transrectal high-intensity focused ultrasound devices: A critical appraisal of the available evidence. J Endourol. 2008;22(2):221-9.
143. Uchida T, Nakano M, Hongo S, Shoji S, Nagata Y, Satoh T, et al. High-intensity focused ultrasound therapy for prostate cancer. Int J Urol. 2012;19(3):187-201.
144. Warmuth M, Johansson T, Mad P. Systematic review of the efficacy and safety of high-intensity focussed ultrasound for the primary and salvage treatment of prostate cancer. Eur Urol. 2010;58(6):803-15.
145. Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: Comparative effectiveness and harms of treatments for clinically localized prostate cancer. Annals of Internal Medicine. 2008;148(6):435-48.
146. Yu T, Luo J. Adverse events of extracorporeal ultrasound-guided high intensity focused ultrasound therapy. PLoS ONE. 2011;6(12).
147. Ahmed HU, Freeman A, Kirkham A, Sahu M, Scott R, Allen C, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol. 2011;185(4):1246-54.
148. Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol. 2012;13(6):622-32.
149. Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset JM, Validire P, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. Eur Urol. 2013;63(4):618-22.
150. El Fegoun AB, Barret E, Prapotnich D, Soon S, Cathelineau X, Rozet F, et al. Focal therapy with high-intensity focused ultrasound for prostate cancer in the elderly. A feasibility study with 10 years follow-up. Int Braz J Urol. 2011;37(2):213-9; discussion 20-2.
151. Mishra S, Sharma R, Garg CP, Muthu V, Ganpule A, Sabnis RB, et al. Preliminary safety and efficacy results with robotic high-intensity focused ultrasound : A single center Indian experience. INDIAN J. UROL. 2011;27(3):331-6.
152. Boutier R, Girouin N, Cheikh AB, Belot A, Rabilloud M, Gelet A, et al. Location of residual cancer after transrectal high-intensity focused ultrasound ablation for clinically localized prostate cancer. BJU International. 2011;108(11):1776-81.
153. Crouzet S, Rebillard X, Chevallier D, Rischmann P, Pasticier G, Garcia G, et al. Multicentric oncologic outcomes of high-intensity focused ultrasound for localized prostate cancer in 803 patients. Eur Urol. 2010;58(4):559-66.
154. Crouzet S, Poissonnier L, Murat FJ, Pasticier G, Rouviere O, Mege-Lechevallier F, et al. Traitement du cancer localise de la prostate avec l'appareil Ablatherm Imagerie Integree : resultats carcinologiques et fonctionnels. Prog Urol. 2011;21(3):191-7.

155. Crouzet S, Chapelon JY, Rouviere O, Mege-Lechevallier F, Colombel M, Tonoli-Catez H, et al. Whole-gland Ablation of Localized Prostate Cancer with High-intensity Focused Ultrasound: Oncologic Outcomes and Morbidity in 1002 Patients. Eur Urol. 2013.
156. Ripert T, Azemar MD, Menard J, Barbe C, Messaoudi R, Bayoud Y, et al. Six years' experience with high-intensity focused ultrasonography for prostate cancer: Oncological outcomes using the new 'Stuttgart' definition for biochemical failure. BJU International. 2011;107(12):1899-905.
157. Ganzer R, Fritsche HM, Brandtner A, Brundl J, Koch D, Wieland WF, et al. Fourteen-year oncological and functional outcomes of high-intensity focused ultrasound in localized prostate cancer. BJU International. 2013.
158. Netsch C, Pfeiffer D, Gross AJ. Development of bladder outlet obstruction after a single treatment of prostate cancer with high-intensity focused ultrasound: Experience with 226 patients. J Endourol. 2010;24(9):1399-403.
159. Netsch C, Bach T, Gross E, Gross AJ. Rectourethral fistula after high-intensity focused ultrasound therapy for prostate cancer and its surgical management. Urology. 2011;77(4):999-1004.
160. Pfeiffer D, Berger J, Gross AJ. Single application of high-intensity focused ultrasound as a first-line therapy for clinically localized prostate cancer: 5-year outcomes. BJU International. 2012;110(11):1702-8.
161. Callea A, Piccinni R, Zizzi V, Sblendorio D, Berardi B, Tempesta A, et al. High-intensity focused ultrasound (HIFU) in prostate cancer: A single centre experience in patients with low, intermediate or high-risk of progression. Archivio Italiano di Urologia e Andrologia. 2010;82(4):253-5.
162. Maestroni U, Dinale F, Minari R, Salsi P, Ziglioli F. High-intensity focused ultrasound for prostate cancer: long-term followup and complications rate. Advances in Urology. 2012;960835.
163. Sung HH, Jeong BC, Seo SI, Jeon SS, Choi HY, Lee HM. Seven years of experience with high-intensity focused ultrasound for prostate cancer: Advantages and limitations. Prostate. 2012;72(13):1399-406.
164. Pinthus JH, Farrokhyar F, Hassouna MM, Woods E, Whelan K, Shayegan B, et al. Single-session primary high-intensity focused ultrasonography treatment for localized prostate cancer: Biochemical outcomes using third generation-based technology. BJU International. 2012;110(8):1142-8.
165. Inoue Y, Goto K, Hayashi T, Hayashi M. Transrectal high-intensity focused ultrasound for treatment of localized prostate cancer. Int J Urol. 2011;18(5):358-63.
166. Komura K, Inamoto T, Black PC, Fujisue Y, Katsuoka Y, Watsuji T, 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.
167. Shoji S, Nakano M, Nagata Y, Usui Y, Terachi T, Uchida T. Quality of life following high-intensity focused ultrasound for the treatment of localized prostate cancer: A prospective study. Int J Urol. 2010;17(8):715-9.
168. Elterman DS, Barkin J, Radomski SB, Fleshner NE, Liu B, Bensimon K, et al. Results of high intensity focused ultrasound treatment of prostate cancer: early Canadian experience at a single center. Can J Urol. 2011;18(6):6037-42.
169. Blana A, Robertson CN, Brown SCW, Chaussy C, Crouzet S, Gelet A, et al. Complete high-intensity focused ultrasound in prostate cancer: Outcome from the @-Registry. Prostate Cancer and Prostatic Diseases. 2012;15(3):256-9.
170. Crouzet S, Murat FJ, Rouviere O, Poissonnier L, Martin X, Colombel M, et al. Oncological outcomes of high-intensity focused ultrasound for localized prostate cancer in 880 consecutive patients. European Urology, Supplements. 2011;10(2):51.
171. Sharifi NMD, Gulley JLMDP, Dahut WLMD. Androgen Deprivation Therapy for Prostate Cancer. JAMA. 2005;294(2):238-44.
172. Albertsen P, Tombal B, Wiegel T, Van Der Meulen E, Persson BE, Olesen TK, et al. Androgen deprivation therapy by a gonadotropin releasing hormone antagonist, degarelix, lowers the risk of cardiovascular events or death when compared to luteinising hormone-releasing agonists. J. Urol. 2013;189(4):e322.

173. Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular Morbidity Associated with Gonadotropin Releasing Hormone Agonists and an Antagonist. Eur. Urol. 2013.
174. Albertsen PC, Nilsson J, Klotz L, Payne H, Van Der Meulen E, Persson BE, et al. Comparision of the risk of cardiovascular events and death in patients treated with degarelix compared with LHRH agonists. J. Clin. Oncol. 2013;31(6).
175. Iversen P, Karup C, Van Der Meulen EA, Tanko LB, Huhtaniemi I. Hot flushes (HF) during androgen deprivation therapy: Direct comparison of monthly degarelix and leuprolide in a phase 3 trial. Ann. Oncol. 2010;21:viii278.
176. Klotz L, Smith M, Persson BE, Olesen TK, Wilde A. Cardiovascular safety of degarelix: RESULTS from a 12-month, comparative, randomized, open-label, parallel-group phase iii trial in prostate cancer Patients. J. Urol. 2010;183(4):e228.
177. See WA, McLeod D, Iversen P, Wirth M. The bicalutamide early prostate cancer program: Demography. Urol. Oncol. 2001;6(2):43-7.
178. See WA, Wirth MP, McLeod DG, Iversen P, Klimberg I, Gleason D, et al. Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: first analysis of the early prostate cancer program. J Urol. 2002;168(2):429-35.
179. Wirth M, Iversen P, McLeod D, See W. Immediate therapy in early prostate cancer: Results from the bicalutamide ('Casodex') EPC programme. Eur. Urol. Suppl. 2002;1(7):20-5.
180. Wirth MP, See WA, McLeod DG, Iversen P, Morris T, Carroll K, et al. 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;172(5 Pt 1):1865-70.
181. Fourcade RO. Nouveaux resultats du programme early prostate cancer 2005. Annales d Urologie. 2006;40(2).
182. Fourcade RO, Richaud P, Brune D, Colombel P, Sarramon JP, Fournier G, et al. Effet du bicalutamide 150 mg, a trois ans de suivi median, dans le cancer de la prostate non metastatique. Prog Urol. 2003;13(3):430-9.
183. Iversen P, McLeod DG, See WA, Morris T, Armstrong J, Wirth MP, et al. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. BJU Int. 2010;105(8):1074-81.
184. Iversen P, Johansson JE, Lodding P, Kylmala T, Lundmo P, Klarskov P, et al. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7.1 years. Scand J Urol Nephrol. 2006;40(6):441-52.
185. Iversen P, Johansson JE, Lodding P, Lukkarinen O, Lundmo P, Klarskov P, et al. 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;172(5 Pt 1):1871-6.
186. Iversen P, Tammela TL, Vaage S, Lukkarinen O, Lodding P, Bull-Njaa T, et al. A randomised comparison of bicalutamide ('Casodex') 150 mg versus placebo as immediate therapy either alone or as adjuvant to standard care for early non-metastatic prostate cancer. First report from the Scandinavian Prostatic Cancer Group Study No. 6. Eur Urol. 2002;42(3):204-11.
187. Wirth M, Tyrrell C, Delaere K, Sanchez-Chapado M, Ramon J, Wallace DM, et al. Bicalutamide ('Casodex') 150 mg in addition to standard care in patients with nonmetastatic prostate cancer: updated results from a randomised double-blind phase III study (median follow-up 5.1 y) in the early prostate cancer programme. Prostate Cancer Prostatic Dis. 2005;8(2):194-200.
188. Wirth M, Tyrrell C, Delaere K, Sanchez-Chapado M, Ramon J, Wallace DM, et al. Bicalutamide (Casodex) 150 mg plus standard care in early non-metastatic prostate cancer: results from Early Prostate Cancer Trial 24 at a median 7 years' follow-up. Prostate Cancer Prostatic Dis. 2007;10(1):87-93.

189. Wirth M, Tyrrell C, Wallace M, Delaere KP, Sanchez-Chapado M, Ramon J, 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;58(2):146-51.
190. Studer UE, Collette L, Whelan P, Albrecht W, Casselman J, de Reijke T, 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;53(5):941-9.
191. Studer UE, Whelan P, Albrecht W, Casselman J, de Reijke T, Hauri D, 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;24(12):1868-76.
192. Studer UE, Whelan P, Albrecht W, Wimpissinger F, Casselman J, De Reijke TM, et al. Immediate or deferred androgen deprivation for patients with prostate cancer and no local treatment of the prostate: Long term results of EORTC 30891. Eur. Urol. Suppl. 2011;10(2):254.
193. Studer UE, Whelan P, Wimpissinger F, Casselman J, de Reijke TM, Knonagel H, et al. Differences in Time to Disease Progression Do Not Predict for Cancer-specific Survival in Patients Receiving Immediate or Deferred Androgen-deprivation Therapy for Prostate Cancer: Final Results of EORTC Randomized Trial 30891 with 12 Years of Follow-up. Eur. Urol. 2013.
194. 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;153(5):1580-6.
195. Akaza H, Homma Y, Okada K, Yokoyama M, Moriyama N, Usami M, et al. Early results of LH-RH agonist treatment with or without chlormadinone acetate for hormone therapy of naive localized or locally advanced prostate cancer: a prospective and randomized study. The Prostate Cancer Study Group. Jpn J Clin Oncol. 2000;30(3):131-6.
196. Akaza H, Homma Y, Okada K, Yokoyama M, Usami M, Hirao Y, et al. A prospective and randomized study of primary hormonal therapy for patients with localized or locally advanced prostate cancer unsuitable for radical prostatectomy: Results of the 5-year follow-up. BJU Int. Suppl. 2003;91(1):33-6.
197. Akaza H, Homma Y, Usami M, Hirao Y, Tsushima T, Okada K, et al. Efficacy of primary hormone therapy for localized or locally advanced prostate cancer: results of a 10-year follow-up. BJU Int. 2006;98(3):573-9.
198. Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, 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;102(11):1531-8.
199. Tombal B, Miller K, Boccon-Gibod L, Schroder F, Jensen JK, Olesen TK, et al. Degarelix vs. leuprolide treatment in patients with advanced prostate cancer: PSA failures during a randomised, phase III trial (CS21). Eur. Urol. Suppl. 2009;8(4):130.
200. Tombal B, Miller K, Boccon-Gibod L, Schroder F, Olesen TK, Persson BE. Degarelix versus leuprolide in prostate cancer patients: New prostate-specific antigen data from a phase III trial (CS21). Eur. J. Cancer Suppl. 2009;7(2-3):411.
201. Tombal B, Miller K, Boccon-Gibod L, Schroder F, Shore N, Crawford ED, et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol. 2010;57(5):836-42.
202. Tombal B, Schroder F, Miller K, Van Der Meulen E, Persson BE. Long-term prostate-specific antigen (PSA) control in prostate cancer: Continuous degarelix or degarelix following leuprolide. Eur. Urol. Suppl. 2011;10(2):335.
203. Tombal B, Schroder F, Olesen TK, Jensen JK, Persson BE. Prostate-specific antigen and alkaline phosphatase control during degarelix or leuprolide treatment. Radiother. Oncol. 2010;96:S116-S7.
204. Boccon-Gibod L, Klotz L, Schroder FH, Andreou C, Persson B, Cantor P, et al. Efficacy and safety of degarelix versus leuprolide

depot (7.5MG) in A 12-month, randomized, open-label, phase III study in patients with prostate cancer. Ann. Oncol. 2008;19(S8):viii198.

205. Crawford ED, Moul JW, Shore N, Van Der Meulen E, Persson BE. Time to progression in patients with prostate cancer: A comparison of continuous degarelix versus degarelix following leuprolide treatment. J. Urol. 2011;185(4):e289-e90.
206. Crawford ED, Moul JW, Shore ND, Olesen TK, Persson BE. Effects on long-term prostate-specific antigen control. J. Urol. 2010;183(4):e262.
207. Crawford ED, Moul JW, Shore ND, Olesen TK, Persson BE. Prostate-specific antigen and serum alkaline phosphatase levels in prostate cancer patients receiving Degarelix or leuprolide. J. Urol. 2010;183(4):e338.
208. Crawford ED, Tombal B, Miller K, Boccon-Gibod L, Schroder F, Shore N, 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;186(3):889-97.
209. Damber JE, Tammela T, Abrahamsson PA, Iversen P, Jensen JK, Olesen TK, et al. Comparing testosterone and PSA for different baseline testosterone concentrations during initiation of degarelix and leuprolide treatment. Eur. Urol. Suppl. 2009;8(4):130.
210. Damber JE, Tammela TL, Iversen P, Abrahamsson PA, Boccon-Gibod L, Olesen TK, et al. The effect of baseline testosterone on the efficacy of degarelix and leuprolide: further insights from a 12-month, comparative, phase III study in prostate cancer patients. Urology. 2012;80(1):174-80.
211. de la Rosette J, Davis R, 3rd, Frankel D, Kold Olesen T. Efficacy and safety of androgen deprivation therapy after switching from monthly leuprolide to monthly degarelix in patients with prostate cancer. Int J Clin Pract. 2011;65(5):559-66.
212. De La Rosette J, Davis RL, Persson BE, Olesen TK. Evaluation of the efficacy and safety of switching from treatment with leuprolide 1-month dosing regimen to degarelix 1-month dosing regimen in prostate cancer (PCA) patients. Eur. Urol. Suppl. 2010;9(2):76.
213. Persson B, Olesen TK, Jensen J, Mason M. Effects of switching from leuprolide to degarelix on long-term prostate-specific antigen (PSA) and serum alkaline phosphatase (S-ALP) control. Ann. Oncol. 2010;21:viii280.
214. Plekhanov A, Crawford ED, Olesen TK, Van Der Meulen EA, Persson BE. Effects on long-term PSA control. Eur. Urol. Suppl. 2010;9(6):538.
215. Shore ND, Moul JW, Crawford E, Olesen T, Persson B. Long-term prostate-specific antigen (PSA) control in prostate cancer (PCa) patients switched from leuprolide to degarelix or receiving continuous degarelix treatment. J. Clin. Oncol. 2010;28(15).
216. Shore ND, Moul JW, Crawford E, Van Der Meulen E, Olesen T, Persson B. Prostate-specific antigen (PSA) progression-free survival (PFS): A comparison of degarelix versus leuprolide in patients with prostate cancer. J. Clin. Oncol. 2011;29(7).
217. Axcrona K, Aaltomaa S, Da Silva CM, Ozen H, Damber JE, Tanko LB, et al. ADT for volume reduction, symptom relief and quality of life improvement in men with prostate cancer: Degarelix versus goserelin plus bicalutamide. Eur. Urol. Suppl. 2012;11(1):e985-ea.
218. Axcrona K, Aaltomaa S, da Silva CM, Ozen H, Damber JE, Tanko LB, et al. Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer: degarelix vs goserelin plus bicalutamide. BJU Int. 2012;110(11):1721-8.
219. Andersson L, Berlin T, Boman J, Collste L, Edsmyr F, Esposti PL, et al. Estramustine versus conventional estrogenic hormones in the initial treatment of highly or moderately differentiated prostatic carcinoma. A randomized study. Scandinavian Journal of Urology & Nephrology Supplementum. 1980;55:143-5.
220. Gospodarowicz MK, Mason M, Parulekar W, Swanson G, Kirkbride P, Brundage M, et al. Final analysis of intergroup randomized phase III study of androgen deprivation therapy (ADT) radiation therapy (RT) in locally advanced prostate cancer (NCIC-CTG, Swog, MRC-UK, INT: T94-0110; NCT00002633). Int. J. Radiat. Oncol. Biol. Phys. 2012;84(3):S4.

221. Warde P, Mason M, Sydes M, Swanson G, Gospodarowicz M, Kirkbride P, et al. Intergroup randomized phase iii study of androgen deprivation therapy (ADT) (plus or minus) radiation therapy (RT) in locally advanced prostate cancer (CAP) (NCIC-CTG, SWOG, MRC-UK, int : 94-0110, NCT 00002633). Radiother. Oncol. 2010;96:S16.
222. Warde P, Mason M, Ding K, Kirkbride P, Brundage M, Cowan R, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet. 2011;378(9809):2104-11.
223. Solberg A, Haugen OA, Viset T, Bergh A, Tasdemir I, Ahlgren G, et al. Residual prostate cancer in patients treated with endocrine therapy with or without radical radiotherapy: a side study of the SPCG-7 randomized trial. Int J Radiat Oncol Biol Phys. 2011;80(1):55-61.
224. Widmark A, Klepp O, Solberg A, Damber JE, Angelsen A, Fransson P, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial.[Erratum appears in Lancet. 2009 Apr 4;373(9670):1174]. Lancet. 2009;373(9660):301-8.
225. Tunn UW, Wiedey K. Safety and clinical efficacy of a new 6-month depot formulation of leuprorelin acetate in patients with prostate cancer in Europe. Prostate Cancer Prostatic Dis. 2009;12(1):83-7.
226. Ishizuka O, Nishizawa O, Nishizawa S, Satoh T, Wajiki M, Kiyokawa H, et al. Comparison of efficacy and safety of 1- and 3-month luteinizing hormone-releasing hormone agonist depots as initial therapies for prostate cancer. Int J Clin Oncol. 2013;18(3):524-30.
227. Desomer A, Dilles T, Steckel S, Duchesnes C, Van Meerbeek M, Peremans L, et al. Dissemination and implementation of clinical practice guidelines in Belgium. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2013. KCE Reports 212 (D/2013/10.273/89). Available from: http://kce.fgov.be/sites/default/files/page_documents/KCE_212_Clinical_practice_guideline_no%20quotes_0_0.pdf
228. Scottish_Government. Prostate Cancer. Clinical Quality Performance Indicators. Scottish Cancer Taskforce; 2012 May 2012. Available from: http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/programme_resources/cancer_qpis.aspx
229. Vlayen J, Stordeur S, Vrijens F, Van Eycken E. Quality indicators in oncology: prerequisites for the set–up of a quality system. Brussels: Belgian Health Care Knowledge Centre (KCE); 2011. Good Clinical Practice (GCP) KCE Report 152 (D/2011/10.273/01)