KCE REPORT 226Cs

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

SUMMARY

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

Belgian Health Care Knowledge Centre

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KCE REPORT 226Cs
GOOD CLINICAL PRACTICE

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Acknowledgements:	Leen Verleye (KCE), Joan Vlayen (KCE) The Guideline Development Group expresses its gratitude to the UK's National Collaborating Centre for Cancer (NCC-C) and National Institute for Health and Care Excellence (NICE). The evidence supporting the majority of the recommendations included in the present guideline is extracted from their source documents.
Other reported interests:	Membership of a stakeholder group on which the results of this report could have an impact: Axel Feyaerts Participation in scientific or experimental research as an initiator, principal investigator or researcher: Bertrand Tombal (president EORTC 60 Group), Dirk Schrijvers (studie Abiraterone acetaat en cabazitaxel), Gert De Meerleer (SBRT for oligo metastates prostateCA), Sandrine Rorive (study biomarkers prostate cancer), Nicolaas Lumen (PI Lomp trial) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Dirk Schrijvers (advisor Janssens Pharmaceuticals en Sanofi), Alain Servaes (Euromut)

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Layout:	Ine Verhulst
Disclaimer:	**The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** **Finally, this report has been approved by common assent by the Executive Board.** **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**
Publication date:	03 July 2014
Domain:	Good Clinical Practice (GCP)
MeSH:	Prostatic Neoplasms; Prostatectomy; Radiotherapy
NLM Classification:	WJ762
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2014/10.273/52
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How to refer to this document?	Tombal B, Desomer A, Jonckheer P, Veereman G, D’Hont C, Van Velthoven R, Feyaerts A, Schrijvers D, Gil T, Renard L, De Meerleer G, Rorive S, Spinnewijn B, Servaes A, Van Damme N, Van Brabandt H. National practice guideline on the treatment of localised prostate cancer – part 2 –Synthesis. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2014. KCE Reports 226Cs. D/2014/10.273/52.
	This document is available on the website of the Belgian Health Care Knowledge Centre.

FORWORD

Alongside breast cancer, prostate cancer is one of the topics that have received priority attention in our studies and rightfully so of course as prostate cancer is the most common type of cancer amongst men. And even though this type of tumour does not tend to be overly aggressive, a number of variants merit homing in on. Some time ago, we produced a guideline on the conservative approach to localised prostate cancer. Now we bring you the second part, which deals with the active treatment of this disease. It goes without saying that KCE is not the only research institution to focus on this particular subject and, rather than reinventing the wheel again, we felt it might be worth seeking out some high-quality existing guidelines. Not surprisingly, we came across a guideline the British National Institute for Health and Care Excellence (NICE) published recently. Aside from being renowned for its impressive production capacity, NICE is also considered to be one of the top institutions in the field of guideline production.

Although most of the NICE findings very much apply to patients in our country, the applicability and acceptability of their recommendations within the Belgian context does warrant meticulous monitoring. As always, KCE has once again been able to count on a group of elite experts in the field to ensure that, in this particular project too, the contextual aspects would be safeguarded. We thank them for their passionate and invaluable input.

Our guidelines are in first instance published with the clinicians who look after the patients affected by this disease in mind. That having been said, increasingly more patients are consulting these sources themselves and use them as a lead to broach the matter with their physician. As several of our recent reports have shown, this is particularly relevant in terms of detecting prostate cancer and of tackling localised cancers but does not in any way prevent the preferences of patients suffering from more advanced tumours being taken into consideration. Proper healthcare increasingly equates to an interaction between conscientious care providers, articulate patients and sound research. Herewith, our contribution to that story...

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

ABSTRACT

1. INTRODUCTION

This report represents part-2 of a Belgian national guideline on the treatment of localised prostate cancer. It is produced by experts appointed by the "College voor Oncologie / Collège de médecins d'Oncologie" in collaboration with the Belgian Health Care Knowledge Centre (KCE), and covers the active treatment options in localised prostate cancer. In part-1 the role of watchful waiting and active surveillance is considered.[1] In a separate related 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]

2. OBJECTIVES AND SCOPE OF THIS GUIDELINE

The present guideline covers the active treatment options in localised prostate cancer. Issues related to diagnosis, follow-up, or the management of relapse after radical treatment are out of scope. No formal cost-effectiveness assessments were conducted.

2.1. Definitions

- 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 tumours extending through the prostate capsule (T3a) as localised, while others would label them as locally advanced disease. In the present guideline the focus is on T1-T2 tumours.
- Prostate-specific antigen (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. Levels of 4 to 10 and 10 to 20 ng/mL are considered slightly and moderately elevated, respectively. PSA levels have to be complemented with other tests to make a firm diagnosis of prostate cancer.[3]

- 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. In the present document reference is made to the 2011 definition.
- Risk stratification: Localised prostate cancer is classified into 3 categories according to the risk of progression by the European Association of Urologists:[4]
  - Low risk: T1-2a AND Gleason <7 AND PSA <10 ng/ml.
  - Intermediate risk: T2b-c OR Gleason 7 OR PSA 10-20 ng/ml.
  - High risk: T3a OR Gleason >7 OR PSA >20 ng/ml.

2.2. Target population

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 partners, general practitioners, radiologists, pathologists, and policy makers.

2.3. Research questions

As a result of an extensive deliberation with stakeholders in 2011, which included a web survey as described earlier,[1] it was decided to focus in this report on the following clinical questions:

- 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.

3. METHODS

3.1. Source guideline

In February 2013 we performed a search for existing guidelines produced by other institutions in order to verify if high-quality recent guidelines that address our clinical research questions were available. This search was carried out in the following databases; the National Guideline Clearinghouse, NICE, SIGN, and G.I.N. additionally, a search for guidelines on websites of oncologic organisations was performed. We identified 30 guidelines that were critically appraised by two independent researchers by using the AGREE-II instrument (www.agreetrust.org). In a first selection round, a rapid assessment was performed based on specific topics from the AGREE domain 3 (Rigour of development): 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"). This resulted in the selection of 15 guidelines that in a next round were fully appraised with the AGREE-II instrument. Based on the final scores the NICE 2008 guideline[5] was judged to be of the highest quality among them.

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" that became available in July 2013[6, 7] along with a full disclosure of the Evidence Review.[8] We used those documents to prepare the present Belgian guideline. In January 2014 NICE eventually published its new guideline ("CG175").[9,10] It comprises a number of recommendations for which the supporting evidence was fully reviewed, whereas for others an update was considered by NICE not to be necessary. The latter decision was based on an assessment conducted by the National Collaborating Centre for Cancer (NCC-C) in April 2011. The NCC-C searched for new evidence using versions of the original search strategies, asking for views of past Guideline Development Group members, and taking into consideration feedback received on the 2008 guideline post publication.[11]

Within the narrow scope of the present Belgian guideline, 18 of NICE's 2014 recommendations were relevant. For 7 out of those 18 recommendations the supporting evidence had been extensively reviewed by NICE until May 2013. For the other 11, NICE decided that a new systematic review was not needed. Of NICE's 18 recommendations, 17 were considered adequate for adaptation to the Belgian context[12] whereas for the one that was related to the use of high-intensity focused ultrasound (HIFU), we performed a new full systematic review ourselves. We also added a *de novo* recommendation on the use of hormones in mono-therapy as explained below.

3.2. *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.

For each research question a standard procedure was followed to retrieve the best evidence. A search for systematic reviews was conducted in MEDLINE, Embase and The Cochrane Library. For HIFU the search window was between February 2008[13] and May 15th, 2013. For hormonal mono-therapy the search start date was 2008 for SRs (with no defined start date for RCTs); the end date was January 22nd, 2014.

If a recent high quality systematic review was available a search for primary studies published after the search date of the review was performed in MEDLINE and Embase. If no systematic review was available a search for primary studies with no date limit was performed in those databases. Members of the guideline development group (GDG) were also consulted to identify additional relevant evidence that may have been missed by the search. Full details about the methodology and the resulting data are provided in the full text report of this guideline.

3.3. Formulation of recommendations

For *de novo* recommendations a first draft was prepared by a small working group based on the retrieved evidence. This working group consisted of the KCE researchers and a few other GDG members (the president and sometimes an extra specialist depending on the topic) who made suggestions via e-mail. The recommendations to be adapted to the Belgian context were copied verbatim (word for word) from the NICE 2014 guideline.[9] This first draft of all recommendations were, 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.

During the meetings, the wording of the recommendations could be altered if deemed necessary, e.g. to increase clarity. More profound changes could also be made if supported by important new evidence. The assessment of the evidence provided by NICE could be judged differently by the Belgian GDG. Every such decision was meticulously notified and reported in the full text of the guideline in a separate paragraph 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 GDG 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 and were also discussed at the May 5th, 2014 meeting on which both stakeholders and GDG members were invited.

To determine the level of evidence (LoE) and strength of recommendation, the GRADE methodology was followed (Tables 1 & 2) for our *de novo* recommendations. For adapted recommendations, i.e. those originating from NICE, a LoE was attributed only to those for which NICE executed a recent evidence review (labelled [2014] in the full text of this report). 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 recommendations for which NICE did not execute a recent evidence review (labelled [2008]), first since no recent evidence update was performed, and second since NICE did not apply the GRADE grading system in 2008.

The strength of a recommendation (SoR) depends on a balance between all desirable and undesirable effects of an intervention, quality of available evidence, values and preferences, and estimated cost (although no formal cost-effectiveness study was conducted). The GRADE procedure to attribute a SoR was used in both the *de novo* and adapted recommendations.

Table 1 – Levels of evidence according to GRADE[14]

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 estimated is limited: the true effect may be substantially different from the estimate of the effect.	RCTs with 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.	

Table 2 – Strength of recommendations according to GRADE[15]

Grade	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).*

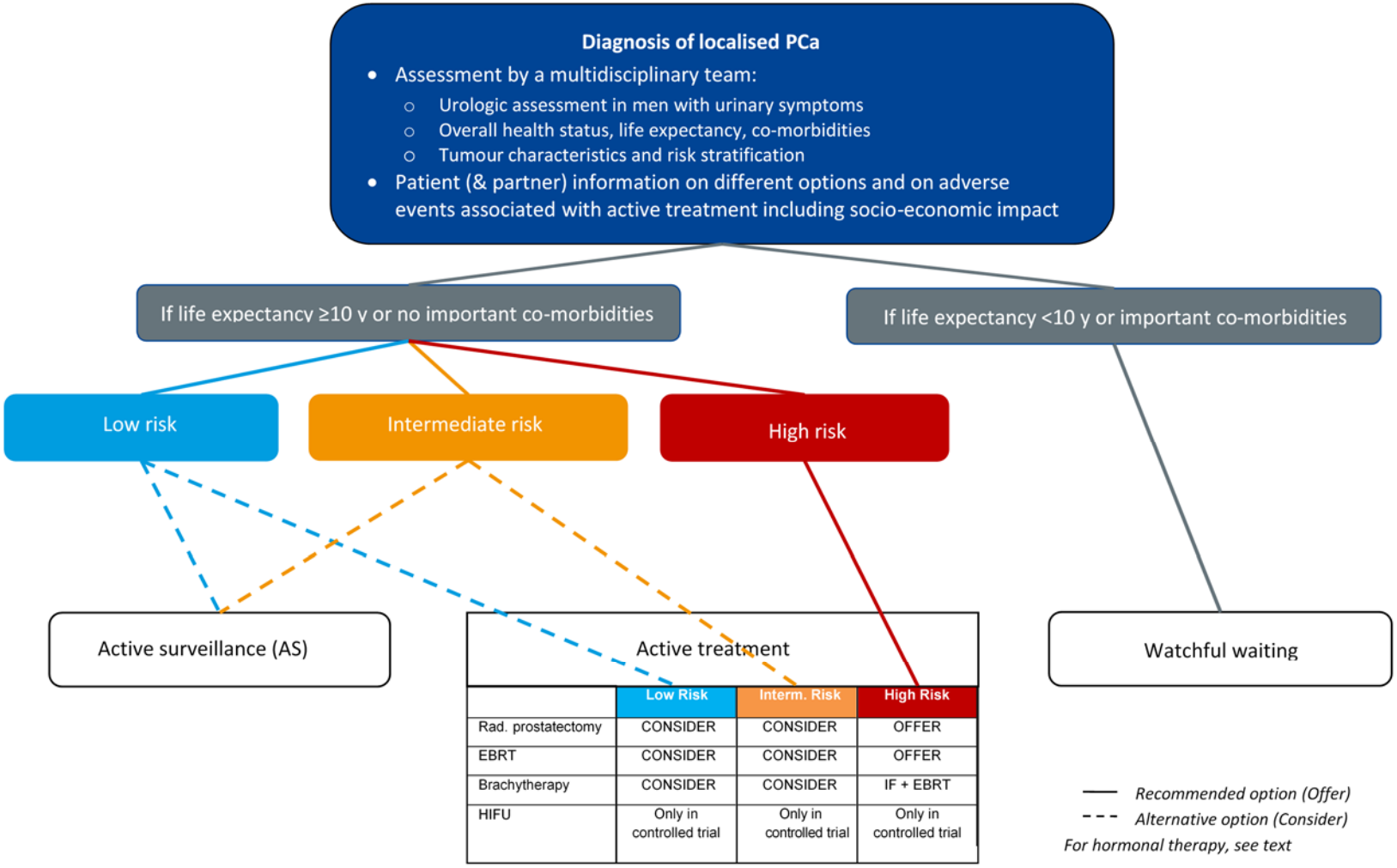
On May 5th 2014, the recommendations prepared by the GDG were submitted to key representatives of professional associations, patients and patient representatives (see colophon) in order to review the draft recommendations on clarity, completeness and acceptability. They rated all recommendations with a score ranging from 1 ('completely disagree') to 5 ('completely agree') and discussed them at a meeting. Minor adaptations to the recommendations could be made if agreed by the president of the GDG and the members that were also invited to attend this meeting. Every such decision was reported in the full text of the guideline in a separate paragraph under the heading "Other considerations".

On May 23th 2014, the guideline was discussed ("external assessment") with 2 independent external experts (cf. names in the colophon) 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.

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

4. 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

5. RECOMMENDATIONS

The details of the evidence used to formulate the recommendations below are available in the scientific report and its supplements. The tables follow the sequence of the chapters of the scientific report.

5.1. 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-economical impact of radical treatment, including potential professional disability and out-of pocket expenses, related to the management of adverse treatment effects.	NA	Strong

5.2. 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.	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

5.3. 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

5.4. 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

6. IMPLEMENTATION AND UPDATING OF THE GUIDELINE

6.1. Implementation

6.1.1. 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.

6.1.2. Patient-centred care

Several recommendations that are formulated in this guideline stress the need to include a patient's (and if he wishes 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.

In a separate recent 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]

6.1.3. Barriers and facilitators for implementation of this guideline

The identification of potential barriers and facilitators related to the use of this guideline was discussed during the stakeholders meeting on May 5th 2014. More information on the identification of barriers and facilitators in guidelines implementation can be found in a recent KCE-report (see KCE website).

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.

6.1.4. 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 professional organisations to their members and to patient advocacy groups. 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.

6.2. 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.[16] 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.[17]

6.3. 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.

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.

POLICY RECOMMENDATIONS[a]

To the College of Oncology

- **Tools should be developed and disseminated to support the implementation of this guideline. This may include presentations of the guideline at professional meetings where the involved disciplines are present.**
- **Assessment of the literature every five years is recommended in order to evaluate the need for updating the guideline. Pending an updated guideline, important new evidence should be listed on the website of the College of Oncology.**

To the responibles of EBMPracticeNet

- **These recommendations should be made available at the point-of-care via the electronic medical record of patients.**

To the scientific and professional associations

- **The implementation of this guideline should be stimulated by the creation of user-friendly tools tailored to the needs of specific groups of caregivers. Various communication channels should be considered such as websites and continuing education seminars.**

Research Agenda

- **A set of quality indicators for the management of prostate cancer in Belgium has to be elaborated.**

[a] The KCE has sole responsibility for the recommendations.

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