KCE REPORT 194B

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

# RECOMMANDATIONS NATIONALES DE BONNE PRATIQUE POUR LA PRISE EN CHARGE DU CANCER LOCALISÉ DE LA PROSTATE : PREMIÈRE PARTIE

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GOOD CLINICAL PRACTICE

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FRANÇOISE MAMBOURG, PASCALE JONCKHEER, JULIEN PIÉRART, HANS VAN BRABANDT

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| **Disclaimer :** | • **Les experts externes ont été consultés sur une version (préliminaire) du rapport scientifique. Leurs remarques ont été discutées au cours des réunions. Ils ne sont pas co-auteurs du rapport scientifique et n'étaient pas nécessairement d'accord avec son contenu.**<br>• **Une version (finale) a ensuite été soumise aux validateurs. La validation du rapport résulte d'un consensus ou d'un vote majoritaire entre les validateurs. Les validateurs ne sont pas co-auteurs du rapport scientifique et ils n'étaient pas nécessairement tous les trois d'accord avec son contenu.**<br>• **Finalement, ce rapport a été approuvé à la majorité par le Conseil d'administration.**<br>• **Le KCE reste seul responsable des erreurs ou omissions qui pourraient subsister de même que des recommandations faites aux autorités publiques.** |
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# PRÉFACE

Le fait que le dépistage systématique du cancer de la prostate au moyen du PSA n'ait pas de valeur ajoutée pour la population masculine fait actuellement l'objet d'un consensus international écrasant. Au contraire, ce dépistage augmente sérieusement le risque d'interventions superflues et par là même, le risque d'incontinence et d'impuissance. Ces conclusions se basent sur l'état de la question issu des études épidémiologiques les plus récentes. Toutefois, certains cliniciens – généralistes et urologues - continuent à prescrire à grande échelle le test du PSA. Des hommes politiques se lancent dans des déclarations insensées sur les bienfaits de l'approche agressive; souvenons-nous ici du discours de l'ex-Maire de New-York, Rudolph Giuliani. Au niveau de notre propre pays, on continue à entendre des plaidoyers pour le dépistage du cancer de la prostate, allant même jusqu'au lancement de nouvelles initiatives de dépistage organisé dans certaines provinces.

En conséquence, de nombreux hommes d'âge moyen ou avancé se voient annoncer des résultats de PSA trop élevés. Ceux-ci sont suivis par des biopsies. Lesquelles mettent régulièrement en évidence des cellules malignes. Même si la plupart de ces patients ayant un petit cancer bien localisé ne nécessitent pas de traitement immédiat, ils se trouvent confrontés à un problème dont ils ne savent que faire. De manière un peu lapidaire, il se résume à ceci : «Monsieur, vous avez un cancer qu'il n'est, en fait, pas nécessaire de traiter. A vous de choisir.»

Dans la pratique, les choses se déroulent d'ailleurs souvent de manière différente, et une prostatectomie radicale est proposée d'emblée. De surcroit, les chiffres provenant des Etats Unis nous montrent que l'arrivée de la chirurgie robotique a entrainé une multiplication de tests PSA et d'opérations de la prostate qui bien souvent n'apportent aucun avantage au patient.

Cette recommandation a été élaborée pour ces hommes auxquels un cancer de la prostate a été diagnostiqué, souvent «par hasard». Nous voulons proposer à leurs médecins des recommandations décrivant une prise en charge justifiée par les connaissances scientifiques les plus récentes en la matière. Il est clair que ni le message ni la décision ne seront jamais simples. C'est pourquoi nous consacrerons une recherche supplémentaire à l'attitude et aux résistances des acteurs concernés. Ajoutons qu'une deuxième partie de cette recommandation, consacrée à la prise en charge des cancers plus avancés est également planifiée.

Cette recommandation ayant été, à l'instar des autres, développée en collaboration avec les membres du Collège d'Oncologie, nous leur adressons nos remerciements pour cette collaboration précieuse.

Raf MERTENS

Directeur Général

# RÉSUMÉ

## INTRODUCTION

Ce travail fait partie d'un projet plus large ayant pour objet la rédaction de recommandations de bonne pratique clinique (RBP) relatives au cancer de la prostate. Ce premier rapport concerne plus particulièrement le rôle de la temporisation (watchful waiting) et de la surveillance active (active surveillance) dans le traitement du cancer de la prostate au stade localisé. La majorité des patients présentant un cancer de la prostate à ce stade ont été diagnostiqué à la suite d'un dosage du PSA et sont asymptomatiques. Certains cancers sont toutefois découverts lors d'une résection endoscopique de la prostate (TURP) pour hypertrophie bénigne. Toutes les recommandations de ce rapport sont basées sur l'efficacité clinique ; aucune analyse du rapport coût-efficacité n'a été réalisée. Ces recommandations ont pour vocation d'être utilisées par l'ensemble des prestataires de soins impliqués dans la prise en charge des patients atteints d'un cancer localisé de la prostate après que le diagnostic ait été posé.

## DÉFINITIONS

Les cancers localisés de la prostate sont définis comme n'ayant pas d'extension au-delà de la capsule prostatique (cT1a -T2c N0M0). Les cancers localisés de la prostate ont tout d'abord été classés en 3 sous-catégories en fonction de leur risque évolutif par d'Amico. Cette classification a été établie selon 3 critères : le stade TNM ; le score de Gleason qui mesure l'agressivité (degré de différentiation) des cellules cancéreuses; la valeur du PSA. La classification utilisée dans ce rapport est la classification utilisée par l'Association européenne d'Urologie (EAU). Elle propose 3 catégories :

- risque faible (T1-2a et Gleason<7 et PSA<10ng/ml)
- risque intermédiaire (T2b-c ou Gleason=7 ou PSA entre 10 et 20 ng/ml)
- risque élevé (T3a ou Gleason>7 ou PSA>20ng/ml).

- **La temporisation (watchful waiting) consiste à retarder le traitement de patients qui ne sont pas candidats à un traitement curatif. Cette stratégie implique de suivre les patients et de leur administrer un traitement à visée palliative au moment de l'apparition des symptômes liés au cancer (obstruction, hématurie, métastases)**
- **La surveillance active (active surveillance) consiste à retarder le traitement de patients candidats à un traitement curatif immédiat. Cette stratégie implique de réévaluer périodiquement l'état d'avancement du cancer et d'administrer un traitement à visée curative en cas de progression de celui-ci.**

L'espérance de vie de la population masculine est extraite des tables belges publiées en 2007-2009. L'espérance de vie d'un individu doit être calculée sur base d'un instrument de mesure validé qui tienne compte des co-morbidités. Le Groupe de développement (GDG) des recommandations a suggéré de laisser le choix de cet instrument aux membres de la COM (Concertation Oncologique Multidisciplinaire).

# QUESTIONS POSÉES

Les recommandations ont été élaborées sur base des réponses aux questions suivantes :

1. Temporisation et surveillance active.

- Quels sont les patients qui peuvent obtenir un bénéfice d'une stratégie de temporisation ou de surveillance active ?
- Les conséquences sur la mortalité, la morbidité ou la qualité de vie de la temporisation ou de la surveillance active d'un cancer localisé de la prostate diffèrent-elles des conséquences d'un traitement curatif immédiat ?

2. Protocole de surveillance active :

- Les différences entre les protocoles induisent-elles des différences de résultats (en termes de mortalité, morbidité ou de qualité de vie)?
- Quelles sont les modalités de la surveillance active?
- Quand est-il nécessaire de passer de la surveillance active à un traitement curatif immédiat ?

# MÉTHODOLOGIE

La méthodologie ADAPTE a été appliquée, ce qui consiste à adapter les RBP (inter)nationales au contexte belge. Une recherche de RBP a été réalisée dans Medline (OVID), EMBASE, le National Guideline Clearinghouse (UK), les sites d'organisations d'élaboration de recommandations et les sites d'organisations spécialisées en oncologie. La qualité des 20 recommandations retenues a été évaluée par deux examinateurs indépendants en utilisant l'instrument AGREE.

Ensuite, pour chaque question clinique, une actualisation des recommandations sélectionnées à été effectuée en se basant sur les données probantes complémentaires identifiées dans les bases de données Medline (OVID), EMBASE et Cochrane Database of Systematic Reviews. Cette recherche de littérature plus récente a été conduite en mai 2012. Sur la base des preuves obtenues, les recommandations finales ont été élaborées par un groupe multidisciplinaire d'élaboration de recommandations (dont les auteurs du présent document). Un niveau de preuve et une force de recommandation ont été attribués à chaque recommandation en utilisant le système GRADE (Tableaux 1 et 2). Ces recommandations ont ensuite été soumises à d'autres experts (stakeholders) dont des représentants des organisations professionnelles. Ceux-ci ont eu l'opportunité de scorer les recommandations et de les discuter lors d'une réunion. Enfin, une validation de ces recommandations a été effectuée par des experts externes sur la base d'une procédure préétablie par le KCE. Les conflits d'intérêt ont été actés.

**Tableau 1 – Niveaux de preuve selon le système GRADE.**

| Niveau de qualité | Définition | Qualité méthodologique des preuves à l'appui |
|---|---|---|
| **Elevé** | Nous sommes très confiants que l'effet réel est proche de l'estimation de l'effet. | RCT sans limitations importantes ou preuves irréfutables provenant d'études d'observation |
| **Modéré** | Nous sommes modérément confiants en l'estimation de l'effet : l'effet réel est probablement proche de l'estimation, mais il y a une possibilité qu'il soit considérablement différent. | RCT comportant des limitations importantes (résultats incohérents, faiblesses méthodologiques, méthodes indirectes ou imprécises) ou exceptionnellement des preuves solides émanant d'études d'observation |
| **Faible** | Notre confiance en l'estimation est limitée : l'effet réel peut être considérablement différent de l'estimation. | RCT comportant des limitations très importantes ou études d'observation ou séries de cas |
| **Très faible** | Nous avons très peu confiance en l'estimation de l'effet : l'effet réel est probablement considérablement différent de l'estimation. | |

**Tableau 2 – Force des recommandations selon le système GRADE.**

| Grade | Définition |
|---|---|
| **Forte** | Les effets bénéfiques de l'intervention l'emportent très certainement sur les risques (*l'intervention est à mettre en pratique*) ou les effets indésirables de l'intervention l'emportent très certainement sur les bénéfices attendus (*l'intervention est à éviter*). |
| **Faible** | Les effets bénéfiques de l'intervention l'emportent probablement sur les risques (*l'intervention est probablement à mettre en pratique*) ou les effets indésirables de l'intervention l'emportent probablement sur les bénéfices attendus (*l'intervention est probablement à éviter*). |

En l'absence de données probantes issues d'essais contrôlés et randomisés, la classification « bonne pratique clinique » (BPC) a été attribuée aux recommandations élaborées en consensus par le groupe multidisciplinaire cité ci-dessus.

# RECOMMANDATIONS CLINIQUES

## Prise en charge

### *Evaluation*

**Bonne pratique clinique**

**Avant toute décision thérapeutique, une évaluation sera effectuée au sein de la Concertation Oncologique Multidisciplinaire, en tenant compte de:**

- **L'état de santé global du patient, son espérance de vie et ses co-morbidités.**
- **La qualité de la biopsie, les caractéristiques et la catégorie de risque de la tumeur.**

### *Information*

**Bonne pratique clinique**

**Il est nécessaire que les patients qui entrent en ligne de compte et optent pour une stratégie à visée curative soient informés des prises en charge communément admises en fonction de leur état de santé, de leur espérance de vie personnelle et de la catégorie de risque de leur tumeur. Ces prises en charge communément admises comprennent (au minimum) la surveillance active, la radiothérapie (externe et interstitielle) et la prostatectomie radicale totale. Les bénéfices et les inconvénients potentiels des différentes options devraient être explicités et discutés avec le patient.**

### *Patients atteints d'un cancer localisé de la prostate (quel que soit le niveau de risque) dont l'espérance de vie est <10 ans*

| Recommandation | Force de la recommandation | Niveau de preuve |
|---|---|---|
| **La temporisation sans projet curatif est l'attitude recommandée pour les patients dont l'espérance de vie est <10 ans ou qui ont des co-morbidités sérieuses.** | **Forte** | **Modéré** |

*Patients atteints d'un cancer localisé de la prostate à risque faible qui entrent en ligne de compte et optent pour une stratégie à visée curative*

| Recommandation | Force de la recommandation | Niveau de preuve |
|---|---|---|
| **La surveillance active devrait être envisagée pour ces patients en tenant compte de leurs préférences et de l'état de leurs fonctions urinaire, sexuelle et digestive.** | **Forte** | **Faible** |
| **Ces patients doivent être informés du fait qu'actuellement le traitement immédiat n'a, par rapport à l'observation, démontré aucun bénéfice après 10-12 ans de suivi.** | **Forte** | **Modéré** |

*Patients atteints d'un cancer localisé de la prostate à risque intermédiaire qui entrent en ligne de compte et optent pour une stratégie à visée curative*

| Recommandation | Force de la recommandation | Niveau de preuve |
|---|---|---|
| **Etant donné les présentations anatomo-pathologiques très variables des cancers de la prostate à risque intermédiaire, aucune recommandation concernant la surveillance active ne peut être formulée actuellement pour ces patients.** | **Forte** | **Faible** |

*Patients atteints d'un cancer localisé de la prostate à risque élevé*

| Recommandation | Force de la recommandation | Niveau de preuve |
|---|---|---|
| **La surveillance active n'est pas recommandée pour ces patients.** | **Forte** | **Faible** |

## Suivi de la surveillance active

### *Biopsie dans l'année qui suit le diagnostic*

| Recommandation | Force de la recommandation | Niveau de preuve |
|---|---|---|
| **Il est recommandé de refaire une biopsie au plus tard un an après le diagnostic du cancer** | **Forte** | **Faible** |

### *Tests*

| Recommandation | Force de la recommandation | Niveau de preuve |
|---|---|---|
| **Les options envisageables dans le suivi sont : un dosage du PSA et une surveillance clinique biannuels ; un ou plusieurs examens d'imagerie annuels.** | **Faible** | **Faible** |

### *Biopsies en routine*

| Recommandation | Force de la recommandation | Niveau de preuve |
|---|---|---|
| **Après avoir réalisé la biopsie à un an, il est recommandé de refaire des biopsies ; le timing optimal de ces biopsies ne peut être défini actuellement.** | **Forte** | **Faible** |

### *Patients dont l'espérance de vie individuelle devient <10 ans en cours de suivi*

| Recommandation | Force de la recommandation | Niveau de preuve |
|---|---|---|
| **Si l'espérance de vie individuelle d'un patient devient <10 ans ou si ce patient atteint l'âge de 80 ans ou s'il développe des co-morbidités sérieuses, il est recommandé d'arrêter la surveillance active et de proposer la temporisation sans projet curatif.** | **Forte** | **Modéré** |

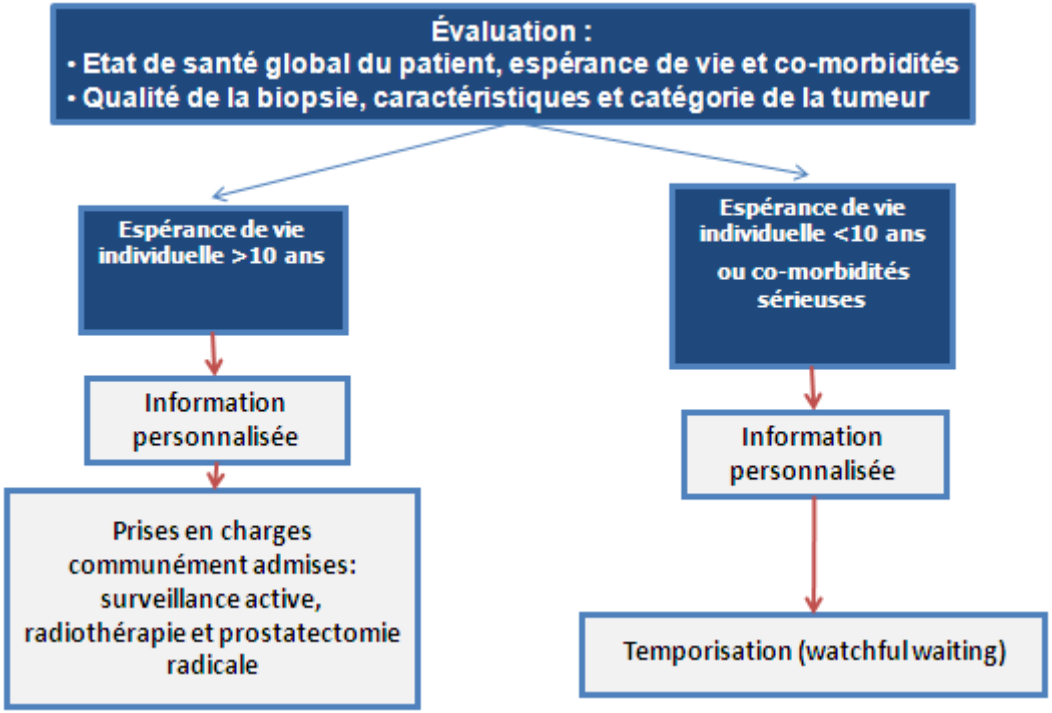
*Progression du cancer*

| Recommandation | Force de la recommandation | Niveau de preuve |
|---|---|---|
| **Toute progression du cancer, suggérée par une valeur du PSA>10ng/ml, un temps de doublement du PSA<3 ans, un changement clinique ou une lésion suspecte à l'imagerie devrait être confirmée par biopsie suivie d'une réévaluation de la catégorie de risque.** | **Forte** | **Faible** |

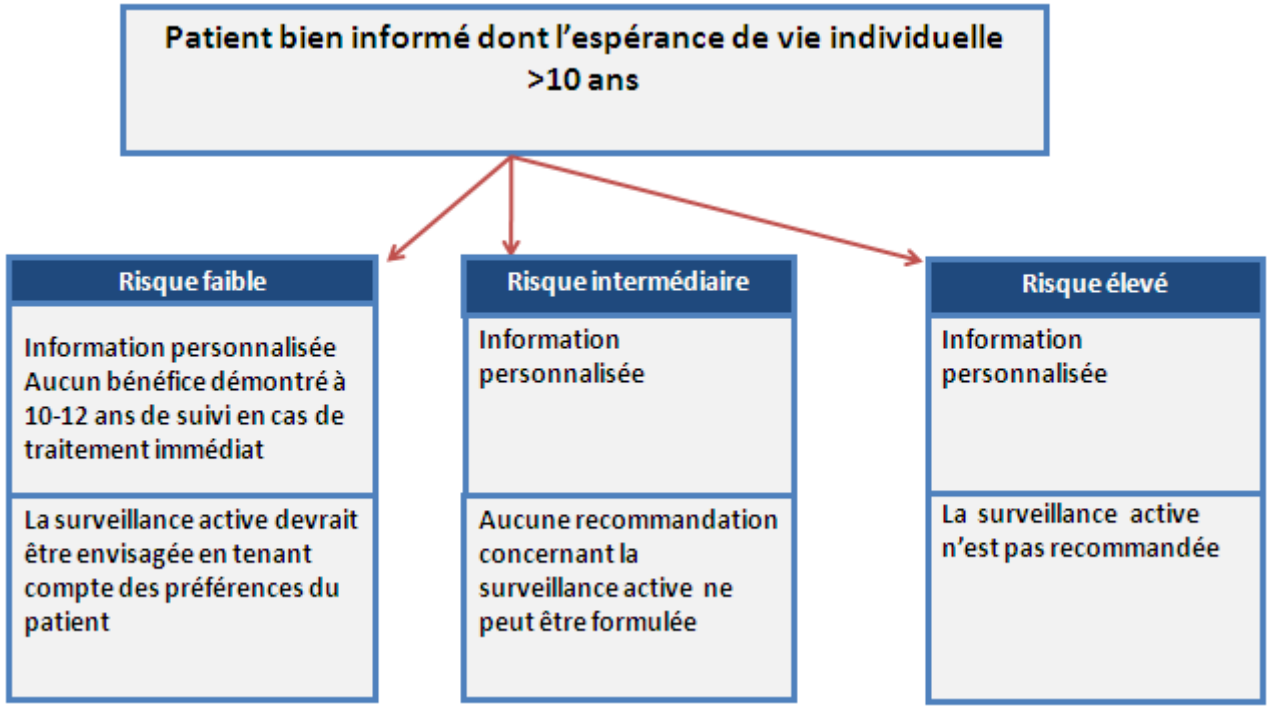
| Bonne pratique clinique |
|---|
| **Le passage de la surveillance active à un traitement curatif immédiat devrait être envisagé en cas de progression de la catégorie de risque.** |

# ARBRE DÉCISIONNEL

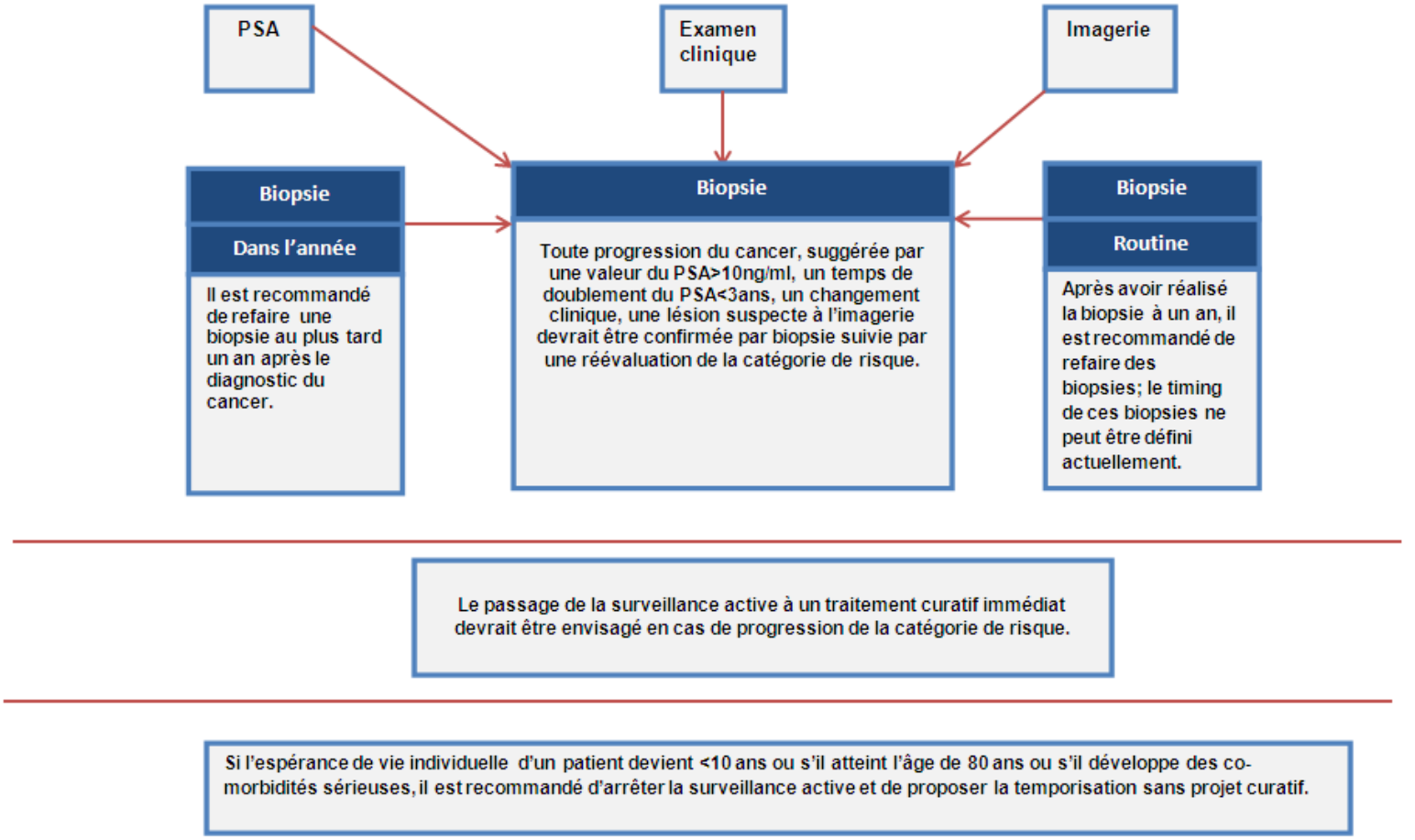
## Prise en charge



Espérance de vie >10 ans



## Suivi de la surveillance active



# MISE EN OEUVRE, ÉVALUATION ET MISE À JOUR

## Mise en œuvre

La mise en œuvre de ces recommandations de bonne pratique clinique sera dirigée par le Collège National d'Oncologie. Un outil de mise en œuvre en ligne, similaire aux outils accompagnant les recommandations précédentes, sera élaboré.

## Mise à jour de la recommandation

Si de nouvelles données probantes primordiales sont disponibles, elles seront mentionnées sur le site Internet du Collège National d'Oncologie et une mise à jour des éléments correspondants de la recherche devrait être envisagée. Une évaluation des recommandations actuelles devrait avoir lieu tous les cinq ans.

# RECHERCHES ULTÉRIEURES

## Qualité de la biopsie

**Il est nécessaire de rédiger un guideline spécifiant les critères de qualité des biopsies (qu'elles soient guidées par échographie ou par résonance magnétique nucléaire (RMN)). (bonne pratique clinique - BPC)**

## Point de vue des patients et des médecins

Un rapport séparé présentera une analyse qualitative des facteurs qui affectent la prise de décision tant des urologues/radiothérapeutes que des patients face aux différentes options de traitement du cancer localisé de la prostate et particulièrement la surveillance active. Cette analyse se basera sur des interviews en face à face de médecins et de patients.

D'autre part, la mise à jour du rapport KCE relatif au dépistage du cancer de la prostate par PSA est en cours.

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# LIST OF ABBREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| AGREE | Appraisal of guidelines for research and evaluation |
| AHRQ | Agency for Healthcare Research and Quality |
| AS | Active surveillance |
| ASA | American Society of Anesthesiology |
| ASAP | Atypical glands suspicious for cancer |
| AUA | American Urological Association |
| CPG | Clinical practice guideline |
| CDSR | Cochrane Database of Systematic Review |
| DRE | Digital rectal examination |
| EAU | European Association of Urology |
| EBRT | External beam radiation therapy |
| ESUR | European Society of Urogenital Radiology |
| GDG | Guideline Development Goup |
| GIN | Guidelines International Network |
| HGPIN | High-grade prostatic intraepithelial neoplasia |
| HR | Hazard ratio |
| HRQoL | Health-Related Quality of Life |
| ISUP | International Society of Urological Pathology |
| mpMRI | Multi-parametric Magnetic Resonance Imaging |
| M-A | Meta-analysis |
| MeSH | Medical Subject Headings |
| MRI | Magnetic Resonance Imaging |
| NICE | National Institute for Health and Clinical Excellence |
| NIH | National Institute of Health |
| NNT | Number needed to treat |
| OMAR | Office of Medical Applications of Research |
| PCOS | Prostate Cancer Outcomes Study |
| PIVOT | Prostate Cancer Intervention versus Observation Trial |

| | |
|---|---|
| PSA | Prostate specific antigen |
| RCT | Randomised controlled trial |
| RP | Radical prostatectomy |
| RT | Radiotherapy |
| RR | Relative Risk |
| SPCG4 | Scandinavian Prostate Cancer Group Study 4 |
| SR | Systematic review |
| TRUS | Transrectal Ultrasonography |
| TURP | Transureteral resection of prostate |
| VACURG | Veterans Administration Cooperative Urological Research Group |
| VIKC | Vereniging Integrale Kankercentra |
| WW | Watchful waiting |

# SCIENTIFIC REPORT

# 1. INTRODUCTION

## 1.1. Definitions

Localised prostate cancer (cT1a-T2c N0 M0) refers to the clinical condition where a cancer is confined to the prostate gland, in the absence of lymph node invasion or metastases, corresponding to a stage N0M0. Prostate cancer (T3a-T4 N0 M0) and any T N+ M0 are considered as loco-regionally advanced prostate cancer.

Gleason score and TNM classification for prostate cancer are shown in Appendix 1.1. Gleason score is the most commonly used system for grading adenocarcinoma of the prostate and is related to the degree of differentiation of the cancer tissue. It can only be assessed using biopsy material. The Gleason score is the sum of the two most common patterns (grades 1-5) of tumour growth found. The Gleason score ranges between 2 and 10, with 10 representing the most aggressive cancers. The correlation between the Gleason score and survival data was first assessed in the VACURG trial.[1]

Localised prostate cancers were first classified by d'Amico based on TNM classification, Gleason score and PSA level (for more details, Appendix 1.3).

Localised prostate cancers (cT1a-T2c N0 M0) are actually classified into 3 categories according to the risk of progression by the European Association of Urologist.[2]

1. Low risk: T1-2a and Gleason < 7 and PSA < 10 ng/ml. This group also contains a subgroup of patients that is presently recognized as "indolent" disease, or very low risk. This includes patients with maximum 2-3 positives biopsy's core from a 12 cores biopsy, each of the positive cores containing maximum 20 to 50% of cancer.
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.

**Epidemiology**

According to the Belgian Cancer Registry, 8.681 new cases of prostate cancer were diagnosed in Belgium in 2009 (< 60y: 1 354, > 60 and < 70y: 2 957, > 70 and < 80y: 3 110, > 80y: 1 260). As in European country, prostate cancer is the most frequent cancer in men in Belgium. Although the yearly number of diagnosed cases increases, the cumulative mortality of prostate cancer remains stable at around 1.1% for men younger than 75 years and at 3.3% for men older than 75 years.[3]

## 1.2. Guideline scope

This study aims to develop a clinical practice guideline (CPG) on the treatment of localised prostate cancer. Importantly, this CPG will not address screening for prostate cancer.

We decided which clinical questions to consider in this guideline after a stakeholders consultation (see point 1.3.1). This guideline will be developed in collaboration with the College of Physicians for Oncology and is intended to be used by all health care providers involved in the care for prostate cancer patients. It was decided to develop a number of consecutive separate reports, each discussing a limited number of clinical questions and recommendations.

### *1.2.1. Stakeholders consultation*

Stakeholders were consulted in 2011. An inventory of relevant clinical questions was built in 4 steps, with the aim of identifying the most problematic issues:

- Step 1: The coordinator of the guideline development group (GDG) of the Oncology College of the Federal Public Service of Public Health sent to KCE experts a list of 28 questions about the following aspects of prostate cancer treatments: active surveillance, radical prostatectomy, external or internal (brachytherapy), beam radiation therapy (EBRT), hormone therapy, bone targeted therapies and chemotherapy. The KCE experts, in concertation with the coordinator then shortened this list to 11 questions identified as the most relevant ones in current Belgian practice.
- Step 2: KCE experts performed a rapid appraisal of existing guidelines and chose the methodological best rating guideline on the AGREE scale (http://www.agreecollaboration.org): the NICE Full Guideline Prostate cancer: diagnosis and treatment (80 recommendations).
- Step 3: The list send by Oncology College and the NICE recommendations were merged and shortened by KCE experts taking into consideration the scope of the guideline, i.e. localised prostate cancer, this ultimately lead to 19 potentially problematic recommendations.
- Step 4: To further limit the number of clinical questions to be scrutinised, the inventory of the 19 potentially problematic recommendations was presented by means of a websurvey, to practitioners involved in prostate cancer care and to patients. Surveyed practitioners were urologists, radiotherapists, general practitioners and nurses in urology. Surveyed patients were members of one Belgian patient association : “Wij ook” and one European association: Europa Uomo. These practitioners and patients were invited by their representatives (5 professional unions, 2 scientific societies and 2 patient groups) to indicate if they agreed or disagreed with the content of each of these 19 potentially problematic recommendations (see the letter and the questionnaire in appendices). Only two alternatives were presented (agree or disagree) to invite the respondents to mark clearly their preferences in one single round. This questionnaire was pre-tested amongst KCE experts (more details in Appendix 2).

Responses were analysed by KCE experts. The discrepancies between the participants’ views were brought to the fore by choosing a threshold of 70% of agreement. Statements with a percentage of agreement inferior to this threshold were considered as problematic statements.

### *1.2.2. Results*

Five themes emerged from the final list of recommendations:

- The role of watchful waiting/active surveillance in the management of localised diagnosed prostate cancer;
- Equivalence of treatment between surgery and radiotherapy in terms of efficacy and side effects;
- Equivalence of different modes of surgery in terms of efficacy and side effects: open surgery, standard laparoscopic surgery, robot-assisted laparoscopic surgery;
- Equivalence of different modes of radiotherapy (external or internal) in terms of efficacy and side effects;
- The place of hormone therapy in the management of localised prostate cancer in relation to operative risk profile, cancer stage and patient characteristics.

**We choose to publish separately the part of the guideline that is focused on the role of watchful waiting/active surveillance in the management of localised prostate cancer.**

# 2. METHODOLOGY

## 2.1. General approach

The present clinical practice guideline CPG was developed by adapting existing international CPGs to the Belgian context. This approach was recently structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers.[4]

The ADAPTE methodology generally consists of three major phases (www.adapte.org):

1. Set-up Phase: Outlines the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources).
2. Adaptation Phase: Assists guideline developers in moving from selection of a topic to identification of specific clinical questions; searching for and retrieving guidelines; assessing the consistency of the evidence therein, their quality, currency, content and applicability; decision making around adaptation; and preparing the draft adapted guideline.
3. Finalisation Phase: Guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

If necessary, included guidelines were updated with more recent evidence.

## 2.2. Clinical questions

This part of the clinical practice guideline addresses the following clinical questions:

1. Who may benefit from watchful waiting or active surveillance? What are the comparative outcomes (in terms of mortality, morbidity and quality of life) of watchful waiting (WW) or active surveillance (AS) versus immediate treatment with curative intent for localised prostate cancer?
2. How is active surveillance (AS) organised?

   Did different active surveillance strategies affect the outcomes?

   How is active surveillance implemented?

   When to switch from AS to curative intervention?

## 2.3. Literature search

### *2.3.1. Search strategy*

The search for was performed step by step.

1. A first search of guidelines was done based on the comprehensive clinical questions.
2. An additional search for meta-analyses (M-A) and systematic reviews (SRs), to perform an update of the best quality guidelines, was done for each specific clinical question.
3. The search was extended to randomised control trials (RCTs) for question 1.
4. The search was extended to observational studies for the question 3 and will be described in this chapter.

To identify published CPGs on prostate cancer, Medline (through OVID), the National Guideline Clearinghouse and specific websites (see 3.1) were searched.

For Medline, the following MeSH or non MeSH terms were used in combination: "prostatic neoplasm" [MeSH Terms] OR prostate cancer [Text Word]. These MeSH terms were combined with a standardised search strategy to identify CPGs. Both national and international CPGs were searched. A language (English, Dutch and French) and date restriction (>2000) were used. CPGs without references were excluded, as were CPGs without clear recommendations.

The search for meta-analysis (M-A) and systematic review (SR) included a search in Medline (through OVID), EMBASE and the Cochrane Database of Systematic Reviews (see Appendix 3.2 for search strings). As for the CPGs, the search was limited to articles published in English, French and Dutch. In general, systematic reviews not reporting the search strategy and/or the quality appraisal of the included studies were excluded. All searches were run between March 2011 and May 2012.

The identified studies were selected based on title and abstract. For all eligible studies, the full-text was retrieved. In case no full-text was available, the study was not taken into account for the final recommendations.

### *2.3.2. Quality appraisal*

#### *2.3.2.1. Clinical practice guidelines*

After exclusion of duplicates, 20 guidelines were found on specific web-site. Two hundred and fifty six publications were retrieved on PubMed (Ovid). Based on title and abstract and after exclusion of duplicates, 17 publications issued from PubMed were selected. Guidelines not focused on watchful waiting and active surveillance and one Japanese guideline not relevant for our population were first excluded. We performed thereafter a rapid appraisal of guidelines quality based on questions 7, 8 and 10 included in AGREE tool.[5] Those questions are focused on selecting the evidence. We consider a good evidence selecting process as a basic requirement and decide not to follow the appraisal if no good description of this process was available. Guidelines were finally scored using the full AGREE-2 tool by two independent researchers (FM and PJ) and discussed in case of disagreement (see Appendix 4.1 for an overview of the scores).

#### *2.3.2.2. Systematic reviews*

The quality of the retrieved SR and M-A was assessed using the checklists of the Dutch Cochrane Centre (www.cochrane.nl). All critical appraisals were done by a single KCE expert (see Appendix 4.2 for an overview of the scores).

#### *2.3.2.3. Randomised controlled trials*

The quality of the retrieved RCTs was assessed using the checklists of the Dutch Cochrane Centre (www.cochrane.nl). All critical appraisals were done by a single KCE expert (see Appendix 4.3 for an overview of the scores).

## 2.4. Data extraction and summary

For each included CPG the following data were extracted: search date and publication year, searched databases, availability of evidence tables, recommendations and referenced evidence.

For each systematic review, the search date, publication year, included studies and main results were extracted. For randomized controlled trials, the following data were extracted: publication year, study population, study intervention and outcomes.

For each clinical question, the recommendations were summarized in data extraction tables. Data extraction tables are provided in Appendix 5. If trial of sufficient quality was found, a level of evidence was assigned to each recommendation and additional study using the GRADE system (see Appendix 6).

## 2.5. Formulation of recommendations

Based on the retrieved evidence, a draft of recommendations was prepared by the KCE team (HV, FM, PJ). This draft together with the data extraction tables were circulated to the guideline development group (see Appendix 9) prior to each face-to-face meeting. The guideline development group met on 2 occasions (06/25/2012, 09/25/2012) to discuss the drafts. Recommendations were changed if important evidence supported this change. Based on the discussion meetings a second and a third draft of recommendations were prepared and send for reviewing to the GDG members.

The recommendations prepared by the guideline development group were circulated to the Professional Associations (see stakeholders list). These panellists received the recommendations one week prior one open meeting (11/27/2012). As a preparation of the meeting all invited panellists were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree' (the panellists were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case a panellist disagreed with the recommendation (score '1' or '2'), (s)he was asked to provide appropriate evidence. All scores (n = 15) were then anonymously summarized into a mean score, standard deviation and % of 'agree'-scores (score '4' and '5') to allow a targeted discussion (see Appendix 9).

# 3. WATCHFUL WAITING VERSUS ACTIVE SURVEILLANCE

## 3.1. Introduction

The long natural history of prostate cancer and the fact that many men diagnosed with prostate cancer may ultimately die from other causes can explain the dilemma one faces in making a choice between an immediate curative treatment and an observational approach with deferred treatment. The latter can be accomplished through two distinctive approaches:

- watchful waiting, which involves a policy of observation and the provision of (palliative) treatment when symptoms arrive; and
- active surveillance which involves close monitoring for biochemical or histological progression with initiation of curative therapy at a given moment.

Unfortunately, the terms watchful waiting and active surveillance are used inconsistently by different authors. Some of them use the terms interchangeably, whereas others draw a clear distinction between them.[6] Original definitions of watchful waiting and active surveillance are summarised by Parker in Table 1.[7]

**Table 1 – Initials definitions of watchful waiting and active surveillance**

| | Active Surveillance | Watchful Waiting |
|---|---|---|
| Primary Aim | To individualize treatment | To avoid treatment |
| Patient Characteristics | Fit for radical treatment; age 50-80 | Age >70 or life expectancy <15 years |
| Tumor Characteristics | T1-T2, Gleason ≤7, Initial PSA <15 | Any T stage, Gleason ≤7, Any PSA |
| Monitoring | Frequent PSA testing, Repeat biopsies | PSA testing unimportant, No repeat biopsies |
| Indications for Treatment | Short PSA doubling time, Upgrading on biopsy | Symptomatic progression |
| Treatment Timing | Early | Delayed |
| Treatment Intent | Curative | Palliative |

## 3.2. Clinical questions

This chapter addresses two questions:

- What are the comparative outcomes (in terms of mortality, morbidity and quality of life) of watchful waiting (WW) and active surveillance (AS) versus immediate treatment with curative intent for localised prostate cancer?
- Who may benefit from watchful waiting or active surveillance?

## 3.3. Selected studies

### *3.3.1. Guidelines*

We selected three guidelines[8-10] of high quality and two[11,2] of moderate quality according to AGREE score. Their recommendations are summarised below. All guidelines included the two RCTs described below.[1, 12]

### *3.3.2. Systematic Reviews*

Two SRs of high quality were selected.[6, 13]

- Wilt published in 2008 a SR aiming to determine the comparative benefits and harms of therapies for clinically localised prostate cancer and how patients and tumour characteristics affect the outcomes of these therapies. This SR was funded by AHRQ and the last search date for RCTs and observational studies was done in September 2007. In this SR, watchful waiting encompasses expectant management or active surveillance. Only 2 randomised trials comparing effectiveness between WW and immediate treatment were selected by the author.[1, 12] VACURG trial and SPCG-4 trial are described in point 3.3.3. None of these RCTs enrolled patients with prostate cancer that was primarily detected by PSA testing. Wilt used also 473 observational studies (>80% cases series). However we could not find how many of them were related to WW. Additional data on harms and patients satisfaction came from the The Prostate Cancer Outcomes Study (PCOS), a large, nationally representative prospective survey of men with localised prostate cancer diagnosed in 1994 or 1995.[14]

- Hegarty published in 2008 one Cochrane SR aiming to compare the beneficial and harmful effects of curative treatment versus WW for the treatment of localised prostate cancer. The systematic search for randomised or quasi-randomised control trials was conducted from 1966 to 30th July 2010. Hegarty retained the two randomised trials selected by Wilt but no observational studies.[6]

Two SRs of moderate quality were also selected.[15, 16]

- The SR published in 2011 by Agency for Healthcare Research and Quality (AHRQ) focused on active surveillance in men with localised prostate cancer. This SR was funded by National Institutes of Health (NIH-US) Office of Medical Applications of Research (OMAR) and the last search date for RCT and observational studies was done in August 2011. This SR found no trial on the effectiveness of AS but 2 updates of VACURG and SPCG-4 trials and 16 cohort studies (mainly retrospective) for other observational management strategies (largely resembling WW). Single-arm AS cohort studies were not included because they could not address comparative effectiveness questions. Moreover, the authors outline the likelihood of confounding by indication in the included cohort studies, due to the differences in patient characteristics and risk profile between patients treated with observational strategies and those who received active treatments. This SR is appraised as of moderate quality because the literature search was focused on Medline and CDSR only, and it's no clear if the quality appraisal of the primary studies was taken into account. Nevertheless, this SR is used here as a basis of process description of AS.[15]
- The SR provided by Farmaka, graded of moderate quality, was also included. This SR was done in order to prepare a Belgian consensus conference on the treatment of a variety of prostate pathologies. One question of the search was: "In which cases, and based on what characteristics, is active surveillance justified as a management strategy in patients with localised prostate cancer?" This SR was funded by INAMI-RIZIV (Belgium) and the search date was August 2010[16]. This SR identified the 2 abovementioned RCT and several observational studies. The authors stressed the very low quality of evidence of the VACURG trial and quoted many limitations of the observational comparative studies (e.g. no clear distinction between WW and AS, wide variety of surveillance protocol, selection of often younger and healthier men). Some cohort studies where the total population was monitored by active surveillance were retained despite their short follow-up period (maximum 7 years) and different active surveillance protocols.

### 3.3.3. Randomised controlled trials

Five RCTs were selected. SPCG-4 and VACURG compared radical prostatectomy with watchful waiting. Although those two studies were included in the SR, we choose to describe them separately because before the publication of the PIVOT trial, they represented the state of the art. Three trials study an active surveillance regimen: one compares expectant management (WW) versus radical prostatectomy (PIVOT) and two focus on active surveillance versus radical prostatectomy or radiotherapy (Protect, Start). Furthermore we found two trials with quality of life as primary outcome, one related to men participating in the UMEA trial and the other to men participating in the SPCG4 trial.[17] The UMEA-1 trial compared the efficacy of external beam radiotherapy versus WW and was conducted between 1986 and 1996 but remains unpublished so far. A long term follow-up focusing on quality of life of the 72 surviving patients was performed in 2001 by Fransson.[18] Several measures of the quality of life of the patients involved in the SPCG4 trial were also performed.[17]

All RCTs are briefly described below.

#### 3.3.3.1. VACURG trial

The VACURG trial started in the pre-PSA screening era and was the first RCT comparing radical prostatectomy versus expectant treatment for early carcinoma of the prostate. This trial started in 1967 and was conducted by Iversen in 15 Veterans Administration Hospitals in U.S. This RCT is appraised as of poor quality because in the absence of bone scan and diagnostic lymphadenectomy in routine evaluation, it is plausible that patients with disseminated disease were enrolled. Furthermore, sample size was small (< 300 participants).[1]

#### 3.3.3.2. SPCG-4 trial

The SPCG-4 started in 1989 and was the second RCT comparing radical prostatectomy (RP) versus watchful waiting (WW). This trial was funded by the Swedish Cancer Society and the National Institutes of Health and was conducted in 14 centres in Sweden, Finland and Iceland.

This RCT of high quality enrolled 695 men at the beginning of the PSA screening era. Patients had newly diagnosed, localised prostate cancer T0d, T1, T2 (following criteria available in 1978). Only 12% of the patients had no palpable T1c tumours at the time of enrolment in the study. Tumours were well or moderately well differentiated and predominantly detected by symptoms, rather than PSA. Patients were relatively young (< 75 years old) with a life expectancy of more than 10 years. WW was strictly defined and included no initial treatment. In the intervention group, the surgery had a radical nature and was not primarily aimed at the preservation of sexual potency. Tumour progression in the watchful waiting group was defined as palpable extracapsular extension or symptoms of obstruction requiring intervention. Hormonal therapy was given if metastases were detected by bone scan or, after 2003, if signs of tumour progression, including elevations of PSA level appeared. Follow-up occurred every 6 months (clinical examination and blood test thereafter) for the first 2 years, then annually (including bone scan and chest x-ray annually before 2003, bone scan every 2 years after).[19] The most recent data issued from SPCG-4 after a follow-up of 15 years were published in 2011 by Bill-Axelson.[12]

#### 3.3.3.3. PIVOT trial

The PIVOT trial is a multicenter RCT comparing radical prostatectomy versus observation for men with localised prostate cancer. This trial was supported by the Department of Veterans Affairs Cooperative Study Program, the US National Cancer Institute and the US Agency for Healthcare Research and Quality (AHRQ). The trial was conducted in 44 Veterans Administration Hospitals and 8 National Cancer Institute sites across the U.S. The primary outcome of this trial was all-cause mortality; secondary endpoints were prostate cancer mortality and the occurrence of bone metastases. This high quality RCT enrolled 731 men with localised prostate cancer from November 1994 through January 2002. 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). In three quarters of the population, the primary reason for biopsy was a PSA elevation or rise. Their mean age was 67 years and the median PSA value was 7.8 ng/mL. Approximately half of tumours (48% in RP group and 49.9% in observation group) were not palpable at digital rectal examination. Follow-up occurred every 6 months (with PSA measurement) for a minimum of 8 years, a maximum 15 years or until death. Quality of life was assessed every year, and bone scan performed every 5 years. In the intervention group (n=364), the technique used for radical prostatectomy, as well as additional interventions were at the surgeon's discretion. In the observation group (n=367), interventions for asymptomatic progression (e.g. change in PSA value) were discouraged. Palliative (non-curative) therapy (TURP, AD and/or targeted RT) was generally reserved for symptomatic or metastatic disease progression.[20]

### 3.3.4. Unpublished randomised controlled trials

#### 3.3.4.1. ProtecT trial

The ProtecT trial is an ongoing multicenter three-arm RCT. It will assess the clinical effectiveness, cost-effectiveness, and acceptability of active monitoring, radical prostatectomy and radical radiotherapy for men with localised prostate cancer. This trial started in 2001 and is conducted in 9 clinical centres in the UK. Recruitment is now complete and over 2500 men with prostate cancer are taking part in the ProtecT trial. The average age of participants is 64 years (range 50 to 80 years). So far, two years of follow up have been completed of a follow-up period of 10-15 years planned. First results should be published after 2015.[21]

#### 3.3.4.2. Start trial

The trial started in 2006 and was conducted in Canada, US, England and Europe. It aimed to compare active monitoring versus radical prostatectomy and (external or internal) radiotherapy for men newly diagnosed with low risk prostate cancer. Unfortunately, this study was stopped early due to poor recruitment.[22] No interim report was published. We contacted the principal investigator of the trial (Chris Parker), who could not provide reasons underlying the poor recruitment

## 3.4. Clinical evidence

### 3.4.1. Mortality

#### 3.4.1.1. Watchful waiting

**Systematic reviews**

- The effect on mortality of interventional treatment vs watchful waiting was based on the SPCG-4 trial in the 4 SRs. They reported that radical prostatectomy improved prostate cancer survival compared with watchful waiting after a median of 8.2 years of follow-up.[23] Meanwhile, more recent recent results from the SPCG-4 study have become available and will be discussed below.
- Two SR added observational studies in their analysis although they differed in their results:[13, 15]
  - Wilt did not formulate a conclusion because of the wide variation across studies (with overlapping overall survival estimates within and between treatments).[13]
  - According to AHRQ, radiotherapy was associated with a lower all-cause mortality rate than watchful waiting.
  - The retrospective studies were also consistent with those of the RCTs and suggested that radical prostatectomy was associated with a lower prostate-cancer-specific mortality than watchful waiting.[15]

**Randomised controlled trials**

- The major results of the low-quality VACURG trial showed not significant difference in median survival.
- After a follow-up of 15 years, the SPCG-4 showed that:[12]
  - All cause mortality

    Radical prostatectomy was associated with a reduction from all cause mortality: RR=0.75 (0.61 to 0.92).

    According to a post hoc statistical sub-group analysis, the NNT to avert one death was 15 overall and 7 for men younger than 65 years of age.
  - Prostate cancer mortality

    Radical prostatectomy was associated with a reduction in the rate of death from prostate cancer: RR=0.62 (0.44 to 0.87).
- After a median follow-up of 10 years, the PIVOT trial[24] showed that:
  - All cause mortality

    Radical prostatectomy did not significantly reduce all-cause mortality: HR=0.88 (0.71 to 1.08); p=0.22.

    According to a preplanned sub-group analysis:[20]

    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).

    Among men with PSA > 10, radical prostatectomy reduced all-cause mortality: HR=0.67 (0.48 to 0.94); p=0.22.
  - Prostate cancer mortality

    Radical prostatectomy did not significantly reduce prostate cancer mortality: HR=0.63 (0.36 to 1.09); p=0.09.

#### 3.4.1.2. *Active surveillance*

**Systematic reviews**

- Each SR mentioned the lack of RCT comparing interventional treatment with active surveillance in localised prostate cancer.
- Two SR added observational studies to consider this issue.[15, 16] Nevertheless they differed in their conclusion:
  - According to AHRQ, evidence was insufficient to evaluate the comparative effectiveness of AS management versus immediate definitive treatment in men with localised prostate cancer (AHRQ). Moreover, the authors underlined the need of a standard definition of AS that clearly distinguishes it from WW.[15]
  - On the basis of cohort studies, the authors of Farmaka concluded that active surveillance in men with early stage prostate cancer was associated with low specific and total mortality rates (maximum follow-up < 7 years). Surveillance active was considered therefore as a possible option in the management of early prostate cancer. The exact place, the type of patients who could get the benefit of this approach and the most suitable monitoring protocol remained to be defined.[16]

### 3.4.2. *Morbidity*

#### 3.4.2.1. *Watchful waiting*

**Systematic reviews**

- The effect of immediate treatment vs watchful waiting on morbidity was based on the SPCG-4 in the SR that considered this question.[6, 13, 15] Based on this RCT, an increased risk for urethral stricture among patients after radical prostatectomy was mentioned. They also quoted an increased relative risk for sexual dysfunction after radical prostatectomy compared with watchful waiting (Hegarty, Wilt). Hegarty reported that after a follow-up of 4 years, radical prostatectomy appeared to increase the risks of erectile dysfunction (RR = 1.78 (1.48 to 2.15)) and urinary leakage (RR = 2.29 (1.63 to 3.22)) although confident statements cannot be made about how frequently these adverse effects occur.[6]
- Two SR added results of observational studies on the morbity analysis:[13, 15]
  - According to the Prostate Cancer Outcomes Study results, inability to attain an erection was higher in men undergoing active intervention, especially androgen deprivation (86%) or radical prostatectomy (58%), than in men receiving watchful waiting(33%).[13]
  - According to AHRQ, men treated with radiotherapy had a higher rates of urinary strictures compared with men on WW.[15]

**Randomised controlled trials**

- After a follow-up of 15 years, the SPCG-4 showed that:[12]
  - The relative risk of distant metastases was lower in the radical prostatectomy group versus the watchful waiting: RR=0.59 (0.45 to 0.79).
  - The relative risk of local progression was lower in the RP group than in the WW: RR=0.34 (20.9 to 0.45).
  - The 1-year cumulative incidence of postoperative complications showed that the most common symptom reported after RP was impotence (58% of patients), followed by urinary leakage (32%).
- After a median follow-up of 10 years, the PIVOT trial [24] showed that:
  - Radical prostatectomy reduced significantly bone metastases: HR=0.40 (0.22 to 0.70); p< 0.001.
  - The perioperative complications occured in 21.4% of men (wound infection was the most common) and included one death.
  - The patient-reported urinary incontinence was significantly more common in the RP group (17%) than in the observation group (6.3%), p< 0.001.
  - The patient-reported erectile dysfunction was significantly more common in the RP group (81.1%) than in the observation group (44.1%), p< 0.001.

#### 3.4.2.2. *Active surveillance*

**Systematic review**

The lack of RCT comparing intervention with active surveillance in localised prostate cancer was also mentioned by the SR broaching the effect on morbidity.[6, 13, 15] Moreover, no observational studies reporting clinical outcomes related to AS as compared to immediate definitive treatment were identified by the authors. AHRQ argued that efficacy results from studies of WW may represent the lower bound of the potential efficacy of AS.

### 3.4.3. *Quality of life*

#### 3.4.3.1. *Watchful waiting*

**Systematic reviews**

- Three SRs broached this question.[6, 13, 15]
- Two SRs mentioned also observational studies:[13, 15]
  - According to the Prostate Cancer Outcomes Study results, patient satisfaction with all selected treatments was high and more than 90% would make the same treatment decision again, and most were delighted or pleased with their treatment decision. However, satisfaction was higher in men who received early intervention than in those who received watchful waiting.[13]
  - No conclusions was formulated in the AHRQ review because the results of observational studies varied across different domains of quality measure for radical prostatectomy and radiotherapy.[15]

**Quality of life trials**

- In the evaluation done by Johansson during the SPCG-4 trial comparing radical prostatectomy with watchful waiting:
  - No difference was found in self-assessed quality of life after more than 10 years between the 2 groups: no difference in number of physical symptoms (RP-WW: 94% vs. 94%).
  - Men were distressed more often by their erectile dysfunction and by urinary leakage when assigned to radical prostatectomy than to watchful waiting. For instance, the RR of distress due to a loss of erection was 1.30 (1.00 to 1.70) and the RR of distress due to urinary leakage was 3.79 (2.36 to 6.06) in the RP group vs the WW.
  - Moreover, the results showed lower scores in all psychological measures in the 2 groups versus a background population. For example, moderate to high level of anxiety were reported by the same proportion of patients in RP (43%) and WW (43%) but by fewer men in the control group (RR for patient group = 1.42 (95% CI: 1.07 to 1.88)).[17]
- In the evaluation done by Fransson during the UMEA-1 trial comparing external beam radiotherapy with watchful waiting :
  - There were no statistically significant differences at 10 years for HR QoL nor urinary trouble (mean 4.8 vs 3.0; p=0.034) nor bowel symptoms.
  - Sexual trouble appear to be more frequent (mean: 7.4 vs. 3.8, p=0.011) after radiotherapy than after watchful waiting (although no difference was found in erectile function nor in maintaining a sufficient erection).[25]

## 3.5. Guidelines recommendations

### 3.5.1. *Patients' point of view*

Patient information was a considerable issue for NICE, AUA and VIKC. All three guidelines wrote specific recommendation therefore (see extraction table in Appendix 5.4.1). This topic was not explicitly mentioned in the EAU guideline. This guideline recommended in fact deferred treatment for all patients not willing to accept side-effects of active treatment. Surprisingly, patients' point of view did nowhere appear in the Spanish guideline.[11]

Furthermore, AUA and NICE underlined the role of patient preferences in treatment decision making: "no one treatment modality is preferable for all patients"[10] and "making treatment decisions, taking into account the effects on quality of life as well as survival".[9]

### 3.5.2. Evolution of concepts

Historical definitions of watchful waiting and active surveillance were presented in point 3.1.

Watchful waiting was traditionally considered in elderly or less fit men to avoid any intervention as long as possible. It excluded radical treatment options.[26] NICE recommends now that men with localised prostate cancer who have chosen a watchful waiting regimen and who have evidence of significant disease progression (rapidly rising PSA level or bone pain) should be reviewed by a physician.[9] It seems that watchful waiting strictly defined is now being replaced by deferred treatment, depending not only on clinical but on biological progression as well. Of note, some guidelines uses the concept of deferred treatment[8, 26] for both curative as palliative treatments.

Conversely, we found no significant evolution of the concept of active surveillance, representing an option for men who are fit for radical treatment in the event of disease progression.[9]

### 3.5.3. Risk assessment

NICE underscores first that an elevated PSA level alone should not automatically lead to prostate biopsy. A decision to take a biopsy must be done taking into account patient preferences, PSA level, DRE findings, and personal risks factors (family history).[9]

After diagnosis, AUA underscores that the first assessment must be extended to the overall health status and the life expectancy of the patient. Specific prostate cancer risk must be assessed on the same time (NICE). Therefore, specific prostate cancer risk strata that are significantly associated with PSA recurrence and cancer-specific mortality were defined. They use PSA, Gleason score and tumour stage. They define prostate cancer as of low, intermediate or high risk. Because variations of this system exist, we use here guidelines specifics definitions in extenso.

### 3.5.4. Treatment

#### 3.5.4.1. Watchful waiting

- The Spanish guideline considers that watchful waiting may be a alternative for low risk localised prostate cancer in patients with limited life-expectancy (< 10 years).[11]
- AUA underlines also that in the SPCG4 trial, radical prostatectomy may be associated with a lower risk of cancer recurrence and cancer specific mortality than watchful waiting.[10] Based on the same trial, EAU recommends deferred treatment **only** for asymptomatic patients with well- or moderately-differentiated cancer, localised or locally advanced prostate cancer and a short life expectancy as for patient with high PSA levels (PSA < 50 ng/mL and PSA doubling time >12 months) for whom cure is unlikely.[26]

#### 3.5.4.2. Active surveillance

- EAU 2012 recommends active surveillance for Stage T1b-T2b patients who are well informed and have well-differentiated prostate cancer and a life expectancy of 10-15 years. Cancers with the lowest risk of progression are: PSA ≤ 10 ng/ml, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, ≤ 50% cancer per biopsy, cT1-2a. For those patients, active surveillance is recommended with a re-evaluation with PSA, TRUS and biopsies.[2]
- VIKC recommends active surveillance for low risk localised (T1c-2a, Gleason< 7, PSA< 10 ng/mL) prostate cancer **only** for patients with limited life-expectancy (older than 75 years).[8]
- The Spanish guideline considers that active surveillance can be offered in patients with clinically localised prostate cancer at low risk, Gleason < 3 + 3, < 50% affected cylinders in the biopsy and PSA < 15 ng/ml. group.[11]

- For AUA also, active surveillance as interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy are appropriate monotherapy treatment options for the patient with low-risk localised prostate cancer (PSA < 10 ng/mL and a Gleason score of 6 or less and clinical stage T1c or T2a).[10]
- NICE recommends that men with low-risk localised prostate cancer who are considered suitable for radical treatment should first be offered active surveillance. A subgroup of men for whom active surveillance is particularly suitable is defined as: men with low-risk localised prostate cancer who have clinical stage T1c, a Gleason score 3+3, a PSA density < 0.15 ng/ml/ml and who have cancer in less than 50% of their total number of biopsy cores with < 10mm of any core involved.[9]
-

**Table 2 – Target population for AS/WW in localised prostate cancer according to guidelines**

| **Watchful waiting or deferred treatment** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Clinical stage** | **Gleason score** | **Serum PSA** | **Biopsy core** | **Life Expectancy** | **Age** | **Other conditions** | **Strength** |
| Aragon | Clinically localised prostate cancer : cT1-cT2, N0-Nx, M0-Mx. | | | | < 10 years | | | Moderate |
| EAU | T1b-T2b | | | | 10-15 years | | Well informed patients | Low |
| EAU | T3-T4 | | PSA< 50ng/ml | | short | | | Low |
| **Active surveillance** | | | | | | | | |
| | **Clinical stage** | **Gleason score** | **Serum PSA** | **Biopsy core** | **Life Expectancy** | **Age** | **Other conditions** | **Strength** |
| EAU | T1a<br>T1c-T2a | < 7 (≤ 6) | ≤ 10 ng/ml | ≤ 2 positive biopsies & ≤ 50% cancer in biopsy | < 10 years<br>< 10 years | | Patients who do not accept treatment-related complications | Moderate |
| VIKC | T1c-2a<br>T3 | < 7 | < 10 ng/ml | | < 10 years | >75 years | Or co morbidities | Low |
| Aragon | Clinically localised prostate cancer : cT1-cT2, N0-Nx, M0-Mx. | 3+3 | < 15 ng/ml | ≤ 50% cancer in biopsy | | | | Very low |
| AUA | T1c or T2a | < 7 | ≤ 10 ng/ml | | | | Patients preferences; health conditions related to urinary, sexual, and bowel function | Low |

| | | | | | | |
|---|---|---|---|---|---|---|
| AUA | T2b | 7 | >10< 20 | | | |
| NICE | T1-T2a<br><br>Particularly if T1c | < 7<br><br>3+3 | < 10 ng/ml<br><br>< 0.15 ng/ml/ml | Cancer in < 50% of tot number of biopsy cores with < 10 mm of any core involved | Men suitable for radical treatment | Low |
| NICE | T2b-T2c | 7 | >10< 20 | | Option | |

## 3.6. Discussion

Clearly, there is a wide variation in the recommendations formulated in the guidelines mentioned above. This may be explained by several mechanisms. As we have shown in this chapter, the body of solid evidence supporting the management of patients with localised prostate cancer is limited. The two oldest RCTs (VACURG and SPCG4) that compared a deferred with an immediate treatment included patients diagnosed before the PSA era. Those patients were symptomatic at the time of diagnosis whereas most actual patients are asymptomatic and diagnosed through a PSA test. The PIVOT trial was more appropriate because three quarters of patients enrolled were diagnosed after a PSA elevation or rise.[24] Unfortunately, this trial compared radical prostatectomy versus *observation*. In the observation group, interventions for asymptomatic progression (e.g. change in PSA value) were discouraged.

Before the publication of the PIVOT trial results, there were no results from RCTs that compared "watchful waiting/observation" with immediate intervention, guideline developers had to rely on observational studies. Obviously these are more prone to bias, which might explain why GDG made different recommendations based on the same studies.

Another explanation why recommendations differ across guidelines may be that guideline developers differ in the relative weight they attribute to the survival benefit obtained from a given strategy and its adverse effects. If a GDG considers prolongation of life as the primordial outcome, it may recommend an interventional strategy whereas the same study may lead another GDG to recommend a more conservative approach because side effects are considered unacceptable compared to a minor survival benefit. The degree to which patient preferences are taken into account may also be an element that explains the observed variations.

## 3.7. GDG assessment

A first draft of the report was discussed on the first GDG meeting (05/25/2012). The GDG underlines that the quality of the biopsy is key for defining the risk category of the prostate cancer. Nevertheless, the clinical pathway leading to the diagnosis of prostate cancer was not considered a priority in this practice guideline (see1.2.2). The following requirements related to the quality of the prostate biopsy and based on a review made by one of the participating pathologist were accepted by GDG consensus:

- The role of the urologist or radiologist:
  - To provide adequate clinical information to the pathologist.
  - To provide adequate tissue samples for pathological examination (12 core biopsies are required, with at least a single prostatic gland per biopsy and average length of prostate tissue > 10 mm per biopsy).
  - To handle the biopsies in a way that will help the pathologist to identify and map cancer in the prostate (separate container for each biopsy is warranted).
- The role of the pathologist:
  - To provide accurate and concise reports using unequivocal terms. Categories of diagnoses should be limited to (1) Benign prostatic gland and stroma, (2) Inflammation, (3) High-grade prostatic intraepithelial neoplasia (HGPIN), (4) Atypical glands suspicious for cancer (ASAP) malignancy cannot definitely be excluded and (5) Prostate cancer.[27] The categories of diseases (3) and (4), i.e. HGPIN and ASAP should never be diagnosed as cancer and never treated as cancer by the clinician.
  - If prostate cancer is diagnosed, the pathology report should include: location and distribution of the tumour, histopathological type, extent of tumour involvement (number of involved cores, linear length of cancer in mm and/or percentage of cancer involvement of each core),[28] Gleason score including primary and secondary patterns (according to the 2005 ISUP Modified Gleason Grading[29]), and if present perineural and/or lymphovascular invasion. The pathologist should refer to the reporting recommendations published by Fine SW et al. (2012) for special Gleason grading scenarios such as the context of abundant high-grade cancer, prostate cancer variants, glomeruloid structures and/or the presence of a tertiary Gleason pattern in prostate biopsies.[30] Perineural and lymphovascular invasion are currently not considered as essential reporting elements for prostate needle biopsies by leading international urological pathologists (more details in Appendix 8). [30]

Although transrectal-ultrasonography (TRUS)-guided biopsy became the accepted standard for PCa diagnosis in the 1990s,[31] the GDG underlined that multiparametric magnetic resonance imaging (mpMRI) may have a role in the diagnosis of localised prostate cancer after a PSA elevation or rise. mpMRI currently includes T1- and T2-weighted images, dynamic contrast, diffusion weighting, and proton spectroscopy.[32] In a recently published SR the accuracy of MRI-guided biopsy was compared to with standard TRUS-guided biopsy. Results from this meta-analysis pooled 16 discrete patient population (n=599) and found that MRI-guided biopsy detects clinically significant cancer in an equivalent number of men versus standard biopsy. This is achieved using fewer biopsies in fewer men. However, methodological limitations of the individual studies and varying definitions of endpoints restrict the external validity of this systematic review. The authors concluded that there is a need for a large study with clearly defined mpMRI criteria, standardised sampling, and a standard definition of clinical significance of a given tumour.[33]

This gap in knowledge has as partly been field by the European Society of Urogenital Radiology (ESUR). It started a process to define recommendations on standardised methods for the detection, localisation, and characterisation of prostate cancer. Those were achieved by a consensus meeting of 16 experts originating from UK, BEL, FR, and NL[32, 34] and contained a unified scoring system for MRI named the Magnetic Resonance Prostate Imaging Reporting and Data System (MR PI-RADS). This scoring system has been validated in 2012 by a French prospective study. This study enrolled 129 men suspected for prostate cancer and referred for MRI after at least one set of negative biopsies. A threshold of ESUR-S ≥ 9 showed the following characteristics: sensitivity: 73.5%; specificity: 81.5%; positive predictive value: 38.2%; negative predictive value: 95.2%; and accuracy: 80.4%. In this situation, the ESUR scoring

system was shown to provide clinically relevant stratification of the risk of showing prostate cancer.[35]

The abovementioned information represent a first start in conducting more robust clinical trials on the efficacy of mpMRI. Although one unpublished modelling study[a] concluded that the use of MRI and MRI–guided biopsies appears to be an efficient strategy, more economic evaluations of this approach for prostate cancer diagnosis will be critical to determine whether this is an efficient approach for risk assessment in all or only selected men presenting with prostate cancer.[36] Results of those study will need to be incorporated in future updates of the present guidelines.

The GDC concludes that a guideline with criteria of a good quality biopsy (as for TRUS-guided as for MRI-guided biopsy) is needed not only for the pathologists but also for the urologists.

Next to cancer-related elements defining the risk category of a given patient, his life expectancy based on his general health status needs to be considered. This may be based on validated life expectancy scale. The GDG suggested leaving the selection of the scale to the discretion of the local team.

Furthermore, men's priorities, needs and concerns are highly related to their family and personal values and need to be considered along the entire disease management.

The guideline development group underlines that the currently most relevant sources of high quality evidence are SPCG4 and PIVOT. Unfortunately, both trials included a "watchful waiting/observation" management and not an active surveillance management. Hence, for the time being, one cannot make any conclusion on the long term effects of any kind of management on low risk non palpable prostate cancer, radical prostatectomy and radiotherapy included. This information should be discussed with the patient before any decision is taken. However, mortality data derived from "watchful waiting" or "observation" trials remain of interest since one can reasonably expect mortality under "active surveillance" management not to exceed mortality observed in patients that were managed under a "watchful waiting/observation" regimen. PIVOT results showed that radical prostatectomy did neither significantly reduce all-cause nor prostate cancer mortality over 10 years as compared to "observation". Moreover, the patient-reported urinary incontinence and erectile dysfunction were significantly more common in the RP group than in the observation group.[24] Therefore, the risk/benefit balance of a radical treatment can be expected to be unfavourable for men with a life expectancy less than 10 years.

**Definitions**

- Watchful waiting consists of deferring treatment in patients with prostate cancer who are no candidate and/or suitable for immediate curative treatment. WW implies following up patients and only treating them with a palliative intent if symptoms appear.
- Active surveillance consists of deferring treatment in patients who are candidate and suitable for immediate curative radical treatment. AS implies revisiting periodically the status of the patient and treating upon progression, still with a curative intent.

Prostate cancer risk categories :

- 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.

[a] The cost-effectiveness of MRI and MRI-guided biopsy versus TRUS-guided biopsy in the diagnosis of prostate cancer: a modelling study. Poster 2012. M.deRooij@rad.umcn.nl

## 3.8. Recommendations

### 3.8.1. Quality of the biopsy

**A guideline with quality criteria of a prostate biopsy is needed not only for pathologists but also for urologists and radiologists *(good clinical practice - GCP)***

### 3.8.2. First assessment

**Before any treatment decision can be made, a assessment should be undertaken including:**

- **the patient's overall health status, his individual life expectancy and comorbidities**
- **the quality of the biopsy and tumour characteristics (including the risk category) (*GCP)***

### 3.8.3. Information

**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. *(GCP)***

### 3.8.4. Men with life expectancy < 10 years

**In patients with localised prostate cancer (all risk category) and individual life expectancy < 10 years or with important comorbidities watchful waiting with palliative intent is recommended. *(strong recommendation, moderate level of evidence)***

### 3.8.5. Low-risk localised prostate cancer

**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. *(strong recommendation, low level of evidence)***

**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. *(strong recommendation, moderate level of evidence)***

### 3.8.6. Intermediate-risk localised prostate cancer

**Because of the pathological heterogeneity of the patients with intermediate-risk localised prostate cancer, no general recommendation can currently be made on active surveillance in this subset of patients.**

### 3.8.7. High-risk localised prostate cancer

**In patients with high-risk localised prostate cancer, active surveillance is not recommended. *(weak recommendation, low level of evidence)***

# 4. DESCRIPTION OF AN ACTIVE SURVEILLANCE MANAGEMENT

## 4.1. Introduction

Based on the GDG's definition of "active surveillance" (see above), the aim of this chapter is to further define the notion of "reassessing periodically the status of the patient and treating with curative intent upon progression".

## 4.2. Clinical questions

This chapter addresses three questions related to the active surveillance (AS) strategy:

1. Do different active surveillance strategies affect outcomes?
2. How is active surveillance implemented?
3. When to switch from AS to another intervention with curative intent?

## 4.3. Studies selected

### *4.3.1. First question*

In 2011, NICE performed an update of its Clinical Guideline[9] in which it expressed concerns over variations in the way active surveillance is being used and performed. Consequently, a new topic on the most effective active surveillance protocol was introduced. The new clinical question was: "In men with prostate cancer followed by active surveillance, is the nature and repetition frequency of surveillance tests (PSA, DRE, MRI, biopsy…) associated with cancer specific survival, overall survival or the rate of radical intervention?" NICE found 14 studies relevant to this clinical question. Although several observational studies were found, no RCT comparing different active surveillance strategies was found in April 2011.[37] We performed an update of NICE's search in August 2012 (see Appendix 3.3). We found no studies comparing different active surveillance strategies. However, we identified 8 observational studies that we considered potentially relevant for questions 2 and 3.[38-43]

### *4.3.2. Second question*

Only three guidelines provided descriptions of active surveillance protocols.[9-11] To obtain more information on the current practice, we studied the 8 abovementioned observational studies. After revision, we excluded case series including less than 400 men. We selected the PRIAS study (Europe),[38] the Johns Hopkins experience (US)[43] and the Canadian experience.[41]

The PRIAS study is an international observational prospective study conducted worldwide since December 2006. This study is facilitated by an electronic Web-based decision tool. Inclusion criteria according to protocol are: clinical stage T1c or T2; Gleason score is ≤ 6, two or fewer biopsy cores invaded with PCa, PSA ≤ 10 ng/mL, PSA density ≤ 0.2 ng/mL. Over 2000 men have been included until now from over 100 participating centres in 17 countries. Risk reclassification on repeat biopsy during the first 4 years of follow-up has occurred in approximately 30% of biopsied men, although a switch towards active therapy has been performed in 22% of the total cohort.[38]

One observational prospective cohort study is conducted at the Johns Hopkins Hospital since January 1995. Inclusion criteria are: very-low-risk cancers, defined by clinical stage (T1c), prostate-specific antigen density < 0.15 ng/mL, and prostate biopsy findings (Gleason score ≤ 6, two or fewer cores with cancer, and ≤ 50% cancer involvement of any core). A total of 769 men have been included until 2011. Curative intervention was recommended on disease reclassification on the basis of biopsy criteria. Overall, 255 men (33.2%) underwent intervention at a median of 2.2 years (range, 0.6 to 10.2 years) after diagnosis. From those, 188 men (73.7%) underwent intervention on the basis of disease reclassification on biopsy.[43]

One prospective single arm cohort study founded by the Canadian Prostate Cancer Research Foundation is conducted in Toronto since November 1995. Inclusion criteria are: clinical stage T1c or T2a; Gleason score ≤ 6, PSA ≤ 10 ng/mL. A PSA doubling time of less than 3 years was considered as an indication for intervention until 2009 and resulted in treatment in 14% of the cohort. Since 2009, a short doubling time has prompted an additional biopsy or mpMRI, and no longer serves as the sole reason for treatment. Upgrading (to Gleason 4+3 or greater) occurred in 8% of the cohort and was an indication for intervention, although,

upgrading to Gleason 3+4 was not. The proportion of patients remained on surveillance was 84, 72, and 62% at 2, 5, and 10 years. One additional result from this study is that for men aged 70 or more, the hazard ratio for non prostate to prostate cancer mortality is 33.3 (95% CI: 8.2 to 136).[41]

We summarised in table 3 below, the active surveillance protocols as described in selected guidelines and in table 4 (4.3.2), the active surveillance protocols as described in the selected observational studies.

**Table 3 – Type and frequency of exams included in active surveillance protocols from clinical guidelines**

| | NICE | | AUA | | Spanish NHS | |
|---|---|---|---|---|---|---|
| | **Investigations** | **Timing** | **Investigations** | **Timing** | **Investigations** | **Timing** |
| History and Physical Exam | Physical examination<br>ECOG Performance status<br>DRE | Every 3 months for 2 years then every 6 months | Physical examination | Periodic | DRE | Every 3 months for 2 years then every 6 months |
| Biochemistry | Serum PSA | Every 3 months for 2 years then every 6 months | Serum PSA | Periodic | Serum PSA | Every 3 months for 2 years then every 6 months |
| Radiology<br>(bone scan, chest x-rays, CTs) | As clinically indicated | - | | | | |
| Other Investigations | TRUS guided biopsy (minimum of 8 cores)<br>Tissue sample from serial needle biopsies for tissue banking | year 1, 4, 7, 10 and then<br>every 5 years | Biopsy | Periodic | Biopsy(10 cylinders at least) | Year 1, 4, and 7 |

*DRE (Digital Rectal Exam)*

**Table 4 - Type and frequency of exams included in active surveillance protocols from observational studies**

| | PRIAS | | Johns Hopkins | | Canada | |
|---|---|---|---|---|---|---|
| | **Investigations** | **Timing** | **Investigations** | **Timing** | **Investigations** | **Timing** |
| History and Physical Exam | Clinical examination | Every 6 months for 2 years, then every year | DRE | Every 6 months | | |
| Biochemistry | Serum PSA | Every 3 months for 2 years then every 6 months | Serum PSA (total and free) | Every 6 months | Serum PSA | Every 3 months for 2 years then every 6 months |
| Radiology (bone scan, chest x-rays, CTs) | Bone scan whenever PSA>20 | - | | | | |
| Other Investigations | Biopsy | At year 1, 4, 7, 10 | Biopsy( 12 to 14 cores) | Every year | Biopsy | After 6-12 months, then every 3-4 years until 80y. |

*DRE (Digital Rectal Exam)*

### *4.3.3. Third question*

Below, we summarise criteria of disease progression described in four guidelines (table 5)[2, 9-11] and in the three selected observational studies (table 6).[38, 41, 43]

**Table 5 – Criteria of disease progression in major practice guidelines**

| | NICE | AUA | EAU | Spanish NHS |
|---|---|---|---|---|
| PSA progression | a) PSA DT < 2 years, based on at least 3 separate measurements over a minimum of 6 months<br>b) Final PSA > 8 ng/ml<br>c) P value < 0.05 from a regression analysis of ln (PSA) on time | | PSA doubling time with a cut-off value ranging between ≤ 2 and ≤ 4 years | PSA velocity>1ng/ml/year |
| Histological progression | Gleason pattern predominant 4 or + (i.e. Gleason 7 (4+3) or higher) in the re-biopsy specimen of the prostate performed at 18 months, 5 years, and 10 years, as per protocol | Increased grade,<br>Increased stage | Gleason score progression ≥ 7<br>At re-biopsy (interval 1-4 years) | Higher degree or greater extension of tumour |
| Clinical progression | a) More than twice increase in the product of the maximum perpendicular diameters of the primary lesion as measured digitally<br>b) Local progression of prostate cancer requiring TURP<br>c) Development of ureteric obstruction<br>d) Radiological and/or clinical evidence of distant metastasis | Increased volume | | Evidence of locally advanced disease in DRE |

**Table 6 - Criteria of disease progression in observational studies**

| | PRIAS | Johns Hopkins | Canada |
|---|---|---|---|
| PSA progression | PSADT< 3 year after a year of inclusion in the study | Not used | PSADT< 3 year |
| Histological progression | Stage>3, Gleason score>6, > 2 biopsy core invaded | Gleason score>6, or > 2 biopsy core invaded, or >50% cancer involvement in any core | Higher Grade |
| Clinical progression | | Reclassification by volume | If unequivocal palpable nodule, biopsy is done |

*Source: observational studies*

## 4.4. Discussion

As we have seen in Chapter 3, the body of scientific evidence in support of one or another management strategy of patients with localised prostate cancer is limited. We found no randomised trials comparing outcomes according to different active surveillance strategies. Consequently, it is impossible to choose the most effective surveillance protocol based on solid data. The variation in inclusion criteria, protocols and patient populations in observational studies preclude a one to one comparison of surrogates and final outcomes.[38]

The reliance on PSA kinetics as the sole reason for treatment is debatable. Loblaw investigated the proportion of patients who would have undergone treatment according to PSA triggers only. Based on the Canadian experience, he found that the proportion of patients who would have had a trigger for treatment ranged from 14% to 42% for histological or clinical progression, versus 37% to 50% for the PSADT triggers and 42% to 84% for the PSA velocity triggers.[44] Consequently, in the Canadian experience, PSA kinetics alone was no longer used as a driver for radical treatment.[41] Surprisingly, a specific protocol adaptation in relation to a patient's age was found only in the Canadian experience. Its protocol included a biopsy every 3-4 years until the patient reached 80. Afterwards, biopsy is no longer performed.

The results of an active surveillance strategy are encouraging so far. However, prospective trials are needed to further optimise the inclusion and follow-up criteria (as the optimal biopsy timing) for active surveillance.[38]

## 4.5. GDG assessment

This draft of the report was discussed on the second GDG meeting (09/25/2012). The GDG underlined that although the body of scientific evidence is limited, the role of the "confirmatory" biopsy is of crucial importance. This is in accordance with Bul who underlined that the short amount of time (median: 1.3 yr) from diagnosis to surgery in the current results of the PRIAS trial (n=2 079) is likely due to reclassification of risk because of understaging or undergrading at diagnosis.[45]

The reliability of the PSA measurements was subject to a discussion. The analysis of the predictive ability of PSA kinetics performed on the prospective cohort conducted at the Johns Hopkins Hospital was cited. In patients included in this cohort who eventually underwent radical prostatectomy, nor PSA velocity (p=0.79) nor PSADT (p=0.87) were associated with the presence of unfavourable surgical pathology.[46] In one other American cohort study cited by the experts, the positive confirmatory biopsy was the only independent predictor of progression: HR 3.16, (95% CI: 1.41 to 7.09, p=0.005).[47] Although new prostate cancer biomarkers may be promising, they were not discussed because of lack of hard evidence so far.

Finally, a consensus was found in accordance to the conclusions of the Canadian experience and others cited above.[41, 46, 47] A change in PSA level or in PSA kinetics may be considered as a trigger to perform more examinations including a biopsy. Nevertheless, disease reclassification and switch to radical treatment must be based on biopsy results.

According to the conclusions of the literature review reporting the absence of valid trials (RCTs) comparing different active surveillance strategies, each team can chose to adopt a protocol including routine biopsy performed at fixed time or a more flexible strategy adapted to each patient. So, a common biopsy protocol such the PRIAS protocol should be considered. Nevertheless, one more flexible protocol keeping in mind the quality of life of the patients, and the anxiety related to the biopsy may also be adopted.

The GDG recommended routine biopsy to be stopped in patients after reaching the age of 80 and in case a patient's life expectancy drops below 10 years. PIVOT results showed us that radical prostatectomy did no reduce prostate cancer mortality over 10 years as compared to "watchful waiting/observation" regimen. For older men (>70 y.), the risk to die from other cause is 33.3 higher than to die from prostate cancer.[41] The mean life expectancy of a man aged of 80 years was 7.22 year in 2007 for Belgium (see Appendix 7).

## 4.6. Recommendations

### 4.6.1. Biopsy one year after the diagnosis

**A repeat biopsy is recommended not later than one year after the diagnosis. *(strong recommendation, low level of evidence)***

### 4.6.2. Other tests

**PSA measurements and clinical examination every six months can be considered. Imaging each year can be considered. *(weak recommendation, low level of evidence)***

### 4.6.3. Routine biopsy

**After the biopsy performed within one year, repeat biopsies are recommended; there timing can currently not be defined. *(strong recommendation, low level of evidence)***

### 4.6.4. Life expectancy < 10y

**In case of the individual life expectancy becomes < 10 year or after reaching the age of 80, or in case of the development of significant comorbidity, it is recommended to stop active surveillance and to offer watchful waiting with palliative intent. *(strong recommendation, moderate level of evidence)***

### 4.6.5. Disease reclassification

**Disease progression as suggested by PSA>10ng/mL, or PSADT< 3 years, or clinical change, or suspicious lesions at imaging, should be confirmed by an additional biopsy and followed by risk reclassification. *(strong recommendation, low level of evidence)***

**Switching to a radical treatment should be considered in case of risk reclassification. *(GCP)***

# APPENDICES

# APPENDIX 1. DEFINITIONS

## Appendix 1.1. Prostate cancer staging

The TNM classification is used to stage prostate cancer. 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 distant spread, or metastasis (M stage). Table 1 below describes TNM classification from Union for International Cancer Control (UICC - www.uicc.org). It represents the 7th edition (TNM-7) of the TNM classification that took effect from January 2010 on, and includes major modifications on PCA as compared to the 6th edition.

**Prostate- 7th edition**

| | |
|---|---|
| T1 Not palpable or visible | |
| T1a | ≤5% or less |
| T1b | >5% |
| T1c | Detected by needle biopsy |
| T2 Confined within prostate | |
| T2a | ≤ half of one lobe |
| T2b | > half of one lobe |
| T2c | Both lobes |
| T3 Through prostate capsule | |
| T3a | Extracapsular |
| T3b | Seminal vesicle(s) |
| T4 Fixed or invades adjacent structures | |
| | No change from 6th |

STAGE GROUPING (ANATOMIC) (UICC)

| | | | |
|---|---|---|---|
| Stage I | T1, T2a | N0 | |
| Stage II | T2b-2c | N0 | |
| Stage III | T3 | N0 | |
| Stage IV | T4 | N0 | |
| | Any T | N1 | |
| | Any T | Any N | M1 |

Change from 6th
Grade was in 6th

Union for International Cancer Control

## Appendix 1.2. Gleason score

The Gleason score is the most commonly used system for grading adenocarcinoma of the prostate. The Gleason score can only be assessed using biopsy material (core biopsy or operative specimens). Cytological preparations cannot be used. The Gleason score is the sum of the two most common patterns (grades 1-5, depending on histologic differentiation) of tumour growth found. The Gleason score ranges between 2 and 10, with 2 being the least aggressive and 10 the most aggressive. In needle biopsy, it is recommended that the worst grade always should be included, even if it is present in < 5% of biopsy material.

## Appendix 1.3. Risk stratification

Localized PCa (T1-T3a N0 M0) are usually separated into 3 categories according **to the risk of progression:**

**Low risk: T1-2a and Gleason< 7 and PSA< 10 ng/ml. This group also contains** a subgroup of patients that is presently recognized as **"indolent" disease, or very low risk**. This includes patients with maximum 2-3 positives biopsies core from a 12 cores biopsy, each of the positive cores containing maximum 20 to 50% of cancer.

**Intermediate risk**: T2b-c or Gleason 7 or PSA 10-20 ng/ml.

**High risk**: T3a or Gleason>7 or PSA>20 ng/ml.

# APPENDIX 2. FIRST STAKEHOLDERS CONSULTATION

## Appendix 2.1. Websurvey “prostate” short list statements

| | Français | Nederlands |
|---|---|---|
| **2. CTscanpelvis** | Il n’est pas recommandé de réaliser un CT scan du pelvis en cas de cancer de la prostate localisé à risque faible ou intermédiaire. | Een CT-scan van het bekken is niet aanbevolen bij mannen met een laag- of intermediair risico gelokaliseerd prostaatCA. |
| **3.Scintigraphier** | Il n’est pas recommandé de réaliser systématiquement une scintigraphie osseuse en cas de cancer de la prostate localisé à risque faible. | Isotopen botscans zijn niet routinematig aanbevolen bij mannen met laag-risico gelokaliseerd prostaatCA. |
| **4. Petscan** | Il n’est pas recommandé de réaliser un examen par émission de positron (PET) en cas de cancer de la prostate localisé à risque faible. | Een PET-scan is niet aanbevolen bij mannen met laag-risico gelokaliseerd prostaatCA. |
| **5.Surveilact** | La surveillance active comprenant la possibilité d’un traitement différé est une stratégie valide dans les cancers localisés à risque faible. | Actieve opvolging met uitstel van behandeling is een valide strategie voor gelokaliseerd laag-risico prostaatCA. |
| **6. IRM** | L’IRM et les marqueurs tumoraux (PCA3 et PSA PHI) sont des stratégies efficaces dans la surveillance active des cancers indolents. | IRM and PCA3-PSA PHI vormen een valide strategie voor actieve opvolging van het “indolent” (slapend) prostaatCA. |
| **7. Prostatectomy** | La prostatectomie radicale et la radiothérapie externe ou interne (brachythérapie) aboutissent aux mêmes résultats d’un point de vue oncologique en cas de cancer localisé à risque faible ou intermédiaire. | Radicale prostatectomie, LDR of HDR brachytherapie en EBRT geven gelijkaardige oncologische resultaten bij patiënten met een laag- of intermediair risico, gelokaliseerd prostaatCA. |
| **8. Prostatectomy_risk** | La prostatectomie radicale et la radiothérapie externe ou interne (brachythérapie) entrainent les mêmes risques de problèmes fonctionnels (dysfonction érectile et incontinence) en cas de cancer localisé à risque faible ou intermédiaire. | Radicale prostatectomie, LDR of HDR bracytherapie en EBRT geven gelijkaardige functionele resultaten (erectie, continentie) bij patiënten met een laag- of intermediair risico, gelokaliseerd prostaatCA. |
| **9. Prostatec_oncoc** | La prostatectomie aboutit aux mêmes résultats d’un point de vue oncologique, quelque soit la technique utilisée (prostatectomie à ciel ouvert, radicale ou assistée par robot) en cas de cancer localisé à risque faible ou intermédiaire. | Open, laparoscopische of robot-geassisteerde radicale prostatectomie geven gelijkaardige oncologische resultaten bij patiënten met een laag- of intermediair risico, gelokaliseerd prostaatCA. |
| **10. Prostatec-alltypes** | La prostatectomie entraine les mêmes risques de problèmes | Open, laparoscopische of robot-geassisteerde radicale |

| | | |
|---|---|---|
| | fonctionnels (dysfonction érectile et incontinence) en cas de cancer localisé à risque faible ou intermédiaire, quelque soit la technique utilisée (prostatectomie à ciel ouvert, radicale ou assistée par robot). | prostatectomie geven gelijkaardige functionele resultaten (erectie, continentie) bij patiënten met een laag- of intermediair risico, gelokaliseerd prostaatCA. |
| **11. HIFU** | Le traitement par HIFU n'est pas recommandé en dehors des études cliniques contrôlées en cas de cancer localisé. | HIFU is niet aanbevolen bij patiënten met gelokaliseerd prostaatCA buiten de context van een gecontroleerde klinische studie. |
| **12. Hormonothérapie** | Une hormono-thérapie (néo)adjuvante est indiquée en combinaison à la radiothérapie externe ou interne (brachythérapie). | (Neo-)adjuvante hormonale therapie is aangewezen in combinatie met EBRT en brachytherapie. |
| **13. Hormono_ Highriskcancer** | Une thérapie hormonale (néo)adjuvante est indiquée en combinaison à la radiothérapie externe ou interne (brachythérapie) en cas de cancer localisé à haut risque. | (Neo-)adjuvante hormonale therapie is aangewezen in combinatie met EBRT en brachytherapie bij patiënten met hoog-risico gelokaliseerd prostaatCA. |
| **14. Hormono_prostatec** | Une thérapie hormonale adjuvante n'est pas indiquée en combinaison à la prostatectomie radicale totale en cas de cancer localisé à haut risque. | Adjuvante hormonale therapie is niet aangewezen in combinatie met radicale prostatectomie bij patiënten met hoog-risico gelokaliseerd prostaatCA. |
| **15. Hormono_étatpatients** | Il est envisageable de traiter par hormonothérapie les patients ayant une tumeur localisée qui ne sont pas en état de subir un traitement local. | Patiënten met gelokaliseerd prostaatCA die niet geschikt zijn voor lokale therapie moeten behandeld worden met hormonale therapie. |
| **16. Hormono_étatpatients_avancés** | Il est envisageable de traiter par hormonothérapie les patients ayant une tumeur localement avancée qui ne sont pas en état de subir un traitement local. | Patiënten met gelokaliseerd gevorderd prostaatCA die niet geschikt zijn voor radicale therapie, moeten behandeld worden met hormonale therapie. |
| **17. Discuss_options** | Il convient que les soignants discutent des différentes options de traitement avec les patients. | Zorgverstrekkers moeten alle relevante behandelings strategieën overleggen met mannen met prostaatCA. |
| **18. Info_effets** | Il convient que les soignants informent les patients des effets du cancer de la prostate et des conséquences potentielles des différents traitements en matière de continence et de sexualité. | Zorgverstrekkers moeten adekwate informatie verstrekken aan mannen met prostaatCA aangaande de effecten van prostaatCA en van de behandelingsopties op de sexuele functie en op de continentie. |
| **19. Discuss_uro§radio** | Vu qu'il existe plusieurs options de traitement et qu'elles peuvent entrainer des effets secondaires sérieux, il convient que les patients qui sont candidats à un traitement radical aient la possibilité de discuter des traitements avec un urologue et un radiothérapeute. | Gegeven de brede waaier van behandelingsmodaliteiten en hun ernstige nevenwerkingen, moeten mannen met prostaatCA die kandidaten voor radicale therapie zijn de kans krijgen om overleg te plegen met een uroloog en een radiotherapeut. |
| **20. Hormono_récidive** | En cas de récidive (PSA) après prostatectomie radicale, un traitement hormonal (de « sauvetage ») est indiqué. | In geval van PSA recidief na radicale prostatectomie is « salvage » hormonale therapie aangewezen. |

## Appendix 2.2. Websurvey “prostate” results

| 1. Groupe-cible | Fréquences | Pourcentages |
|---|---|---|
| Urologue | 54 | 60,0% |
| Radiothérapeute | 13 | 14,4% |
| Généraliste | 10 | 11,1% |
| Infirmier(ère) en urologie | 3 | 3,3% |
| Patient | 10 | 11,1% |
| Total/ répondants | 90 | |

*Interrogés : 90 / Répondants : 90 / Réponses : 90. Pourcentages calculés sur la base des répondants*

| 2. CTscanpelvis | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 48 | 53,9% |
| Pas d'accord | 41 | 46,1% |
| Total | 89 | 100,0% |

| 3. Scintigraphie | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 79 | 88,8% |
| Pas d'accord | 10 | 11,2% |
| Total | 89 | 100,0% |

| 4. Petscan | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 88 | 98,9% |
| Pas d'accord | 1 | 1,1% |
| Total | 89 | 100,0% |

| 5. Surveilact | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 83 | 93,3% |
| Pas d'accord | 6 | 6,7% |
| Total | 89 | 100,0% |

| 6. IRM | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 38 | 44,7% |
| Pas d'accord | 47 | 55,3% |
| Total | 85 | 100,0% |

| 7. Prostatectomy | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 58 | 65,9% |
| Pas d'accord | 30 | 34,1% |
| Total | 88 | 100,0% |

| 8. Prostatectomy_risk | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 20 | 23,0% |
| Pas d'accord | 67 | 77,0% |
| Total | 87 | 100,0% |

| 9. Prostatectomy_onco | F Fréquences | Pourcentages |
|---|---|---|
| D'accord | 69 | 79,3% |
| Pas d'accord | 18 | 20,7% |
| Total | 87 | 100,0% |

| 10. Prostatectomy_alltypes | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 45 | 51,1% |
| Pas d'accord | 43 | 48,9% |
| Total | 88 | 100,0% |

| 11. HIFU | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 83 | 94,3% |
| Pas d'accord | 5 | 5,7% |
| Total | 88 | 100,0% |

| 12. Hormonothérapie | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 27 | 31,4% |
| Pas d'accord | 59 | 68,6% |
| Total | 86 | 100,0% |

| 13. Hormono_highriskcancer | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 79 | 89,8% |
| Pas d'accord | 9 | 10,2% |
| Total | 88 | 100,0% |

| 14. Hormono_prostatectomy | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 57 | 67,1% |
| Pas d'accord | 28 | 32,9% |
| Total | 85 | 100,0% |

| 15. Hormono_étatpatients | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 36 | 41,4% |
| Pas d'accord | 51 | 58,6% |
| Total | 87 | 100,0% |

| 16. Hormono_étatpatients_avancé | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 75 | 85,2% |
| Ppas d'accord | 13 | 14,8% |
| Total | 88 | 100,0% |

| 17. Discuss_options | Frequency | Pourcentages |
|---|---|---|
| D'accord | 88 | 98,9% |
| Pas d'accord | 1 | 1,1% |
| Total | 89 | 100,0% |

| 18. Info_effets | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 88 | 100,0% |
| Total | 88 | 100,0% |

| 19. Discuss_uro&radio | Fréquences | Pourcentages |
|---|---|---|
| D'accord | 69 | 78,4% |
| Pas d'accord | 19 | 21,6% |
| Total | 88 | 100,0% |

| 20. Hormono_récidive | F Fréquences | Pourcentages |
|---|---|---|
| D'accord | 36 | 41,9% |
| Pas d'accord | 50 | 58,1% |
| Total | 86 | 100,0% |

| 22. Language | Fréquences | Pourcentages |
|---|---|---|
| FR | 37 | 41,1% |
| NL | 53 | 58,9% |
| Total | 90 | 100,0% |

# APPENDIX 3. LITERATURE SEARCH

## Appendix 3.1. Clinical practice guidelines

### *Appendix 3.1.1. Sources*

A broad search of electronic databases (Medline, EMBASE), specific guideline websites and websites of oncologic organisations (Table 7) was conducted in February 2011. Only guidelines published in Dutch, English, French or German and after 01/01/2005 were selected.

**Table 7–Searched guideline websites and websites of oncologic organisations**

| | | |
|---|---|---|
| **0** | Alberta Heritage Foundation For Medical Research (AHFMR) | http://www.ahfmr.ab.ca/ |
| **0** | American Society of Clinical Oncology (ASCO) | http://www.asco.org/ |
| **0** | American College of Surgeons (ACS) | http://www.facs.org/cancer/coc/ |
| **5** | CMA Infobase | http://mdm.ca/cpgsnew/cpgs/index.asp |
| **15** | Guidelines International Network (GIN) | http://www.g-i-n.net/ |
| **1** | National Comprehensive Cancer Network (NCCN) | http://www.nccn.org/ |
| **1 new, 5 ACR** | National Guideline Clearinghouse | http://www.guideline.gov/ |
| **0** | National Cancer Institute | http://www.cancer.gov/ |
| **1 duplicate** | Haute Autorité de Santé (HAS) | http://bfes.has-sante.fr/HTML/indexBFES_HAS.html |
| **0** | BC Cancer Agency | http://www.bccancer.bc.ca/default.htm |
| **10 on screening** | Institute for Clinical Systems Improvement (ICSI) | http://www.icsi.org/index.asp |
| **1 (all)** | National Health and Medical Research Council (NHMRC) | http://www.nhmrc.gov.au/ |
| **0** | Scottish Intercollegiate Guidelines Network (SIGN) | http://www.sign.ac.uk/ |
| **2 duplicate** | New Zealand Guidelines Group (NZGG) | http://www.nzgg.org.nz/ |
| **1 HAS + update (all)** | Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) | http://www.fnclcc.fr/sor/structure/index-sorspecialistes.html |
| **5 duplicate** | National Institute for Health and Clinical Excellence (NICE) | http://www.nice.org.uk/ |

### *Appendix 3.1.2. Search terms for Medline (Ovid)*

For Medline the following MeSH or non MESH terms were used in combination: "prostatic neoplasms"[MeSH Terms] OR prostate cancer[Text Word]. For EMBASE the following Emtree terms were used in combination: ”prostate cancer, watchful waiting”. These MeSH and Emtree terms were combined with a standardised search strategy to identify CPGs (Table 8).

**Table 8 – Standardised search strategy for CPGs**

| Database | Search strategy |
|---|---|
| **Medline** | guideline [pt] OR practice guideline [pt] OR recommendation* [ti] OR standard* [ti] OR guideline* [ti] |
| **EMBASE** | 'practice guideline'/exp |

Exclusion criteria : advanced stage :

Medline (Ovid) search :

prostatic neoplasms.mp. or Prostatic Neoplasms/ (73381)

2 prostate cancer.mp. (47158)

3 Guideline/ or Practice Guideline/ (20402)

4 "recommendation*".m_titl. (17706)

5 "standard*".m_titl. (52575)

6 "guideline*".m_titl. (36194)

7 1 or 2 (79090)

8 3 or 4 or 5 or 6 (113470)

9 7 and 8 (632)

10 limit 9 to (humans and yr="2005 -Current" and (dutch or english or french or german)) (256)

### *Appendix 3.1.3. Results*

After exclusion of duplicates, 20 guidelines were found on specifics web-site. Two hundred fifty six publications were retrieved on Pubmed (Ovid). Based on title and abstract and after exclusion of duplicates, 17 publications issued from Ovid were selected. Finally, we found 37 guidelines. Some guidelines are focused on specific questions. Therefore, they are presented by topics on Table 9. First column shows guidelines what take all the prostate cancer process into account. Second column shows guidelines focused on prostate cancer diagnosis. Third column shows guidelines focused on all prostate cancer treatment. Column five shows guidelines focused on prostate cancer follow-up, column six on prostate cancer by men > 70y and column seven on news technologies.

**Table 9 – All guidelines found by topics (first selection)**

| All | Diagnosis | | | Treatment | | | | | T3 | Follow-up | Senior 70 y | HIFU/cryo |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Biopsy | PET/FDG | Bone scan | Radical | Brachy | IMRT | Combined | Quality of Life | | | | AUA |
| **NICE 2008** | NICE 2010 | Bourguet 2007 | Briganty | | ACR | Maceira Rozas 2006 | NZGG | Casas | | | Droz JP | |
| **NovaScotia 2006** | Bertaccini 2007 | | | CCO | NICE Low | CCO | Sidhom 2008 | | | McIntosh | Mongiat-Arthus | CCO |
| **Saska 2008** | CMA 2009 | | | | NICE High (174) | | Hoffman | | | Richaud 2005 | | NICE |
| **EAU 2010 (Heidenrich)** | | | | | IQWIG | | | | | Roach | | NICE |
| **AUA (20)** | | | | | Kovacks 2005 | | | | | | | |
| **VIKC, De Reijke 2008** | | | | | | | | | | | | |
| **ESMO, Horwich 2008** | | | | | | | | | | | | |
| **Kamidono 2008** | | | | | | | | | | | | |
| **NCCN 2010** | | | | | | | | | | | | |
| **S3, Wenz** | | | | | | | | | | | | |

We excluded for this part 26 guidelines outside of the scope. We performed first a rapid appraisal of 11 guidelines quality based on questions 7,8 and 10 included in AGREE tool. Those questions are focused on selecting the evidence .

Table 4 – Rapid appraisal based on Questions 7, 8, 10 of AGREE (version May 2009 and scale 1 to 7)

| Reference | Q 7 : Systematic methods were used to search evidence | Q 8 : The criteria for selecting the evidence were clearly described | Q 10 : The methods used for formulating recommendations were clearly described | Conclusion |
|---|---|---|---|---|
| **NICE 2008**<br>**Made by NCC-C Lit search: 1 June 2007** | 7 | 7 | 7 | 21/21, included |
| **NovaScotia 2006** | 1 | 1 | 1 | Methodology not described<br>excluded |
| **Saskatchewan Cancer Agency Update 2008** | 1 | 1 | 1 | Methodology not described, decisions based on consensus<br>excluded |
| **AUA 2007**<br>**Lit search: April 2004** | 7 | 6 | 6 | 19/21, included |
| **HAS, (SOR)update 2008** | 6 | 1 | 1 | Excluded (after expert discussion) |
| **EAU 2010**<br>**Lit search: update janv 2010** | 6 | 4 | 5 | 15/21: tentatively included |
| **VIKC, De Reijke 2008** | 5 | 6 | 6 | 19/21, included |
| **ESMO** | 1 | 1 | 1 | Methodology not described<br>excluded |
| **Kamidono** | 5 | 6 | 3 | 14/21: excluded |
| **NCCN (2010)** | 1 | 1 | 1 | Excluded |
| **Aragon (2011)** | 6 | 4 | 4 | 14/21: tentatively included |

We considered a good evidence selecting process as a basic requirement and decided not to follow the appraisal if no good description of this process was available. Then, we performed the appraisal of the 5 (tentatively) included guidelines with the entire AGREE tool (see point 4.1).

## Appendix 3.2. Systematic reviews and primary studies for question 1

P: localized prostate cancer

I: active surveillance or watchful waiting

C: other treatment

O : mortality, morbidity, quality of life

### *Appendix 3.2.1. Medline*

Keywords

- MeSH : Prostatic Neoplasms :Tumours or cancer of the PROSTATE.
- Prostatic Neoplasms/th : therapy of Tumours or cancer of the PROSTATE
- PROSTATECTOMY : Complete or partial surgical removal of the prostate. Three primary approaches are commonly employed: suprapubic - removal through an incision above the pubis and through the urinary bladder; retropubic - as for suprapubic but without entering the urinary bladder; and transurethral (TRANSURETHRAL RESECTION OF PROSTATE).
- Text: *Watchful Waiting

| | |
|---|---|
| **Project number** | 2011-01-GCP |
| **Project name** | Prostate cancer |
| **Search question(s)** | Role of active surveillance/watchful waiting in the management of localised prostate cancer (low, intermediate and high risk)? |
| **Structured search question(s) (PICO, SPICE, ECLIPSE, ..)** | and related keywords |

| | | |
|---|---|---|
| **P (patient)** | Patient with localised prostate cancer | "Prostatic neoplasms" or local$ prostate cancer |
| **I (Intervention)** | active surveillance/watchful waiting | *Watchful Waiting or active surveillance |
| **C (comparison)** | Surgery or other treatment | Prostatectomy/ |
| **O (outcome)** | Mortality, morbidity, quality of life | |

| | |
|---|---|
| **Date** | 07/12/2011 |
| **Database** | Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2011 |
| **Search Strategy** | Prostatic Neoplasms/ (54530)<br>2 local$ prostate cancer.mp. (3900)<br>3 1 or 2 (54655)<br>4 watchful waiting.mp. or *Watchful Waiting/ (1289)<br>5 androgen antagonists.mp. or Androgen Antagonists/ (5198)<br>6 brachytherapy.mp. or Brachytherapy/ (10409)<br>7 neoadjuvant therapy.mp. or Neoadjuvant Therapy/ (8440)<br>8 prostatectomy.mp. or Prostatectomy/ (14223)<br>9 radiotherapy.mp. or Radiotherapy, Intensity-Modulated/ or Radiotherapy/ or Radiotherapy, Conformal/ (84353)<br>10 5 or 6 or 7 or 8 or 9 (110055)<br>11 exp Controlled Clinical Trial/ (37584)<br>12 exp Randomized Controlled Trials as Topic/ |

| | |
|---|---|
| | (67539)<br>13 exp Random Allocation/ (37598)<br>14 exp Double-Blind Method/ (67080)<br>15 exp Single-Blind Method/ (12779)<br>16 exp Clinical Trial/ (446179)<br>17 (clin$ adj25 trial$).tw. (152122)<br>18 ((single or double or triple or treble) adj25 (blind$ or mask$)).tw. (67282)<br>19 placebo$.tw. (85758)<br>20 random$.tw. (402126)<br>21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (822281)<br>22 (watchful waiting$ or observation$ or expectant management$ or careful monitoring$ or surveillance$ or delay$ or deferred treatment$ or no initial treatment$).tw. (477802)<br>23 (watch and wait$).tw. (265)<br>24 22 or 23 (478011)<br>25 4 or 24 (478117)<br>26 3 and 10 and 21 and 25 (455) |
| **Note** | 18 (5 on quality of life) remained before critical appraisal |

## *Appendix 3.2.2. Cochrane Library*

| | |
|---|---|
| **Date** | From 2007 until 07/01/2011 |
| **Database** | CDSR, DARE, CCRCT |
| **Search Strategy (MESH term)** | Prostatic Neoplasms/th |
| **Note** | CDSR (6), DARE(5), CCRCT (60), total : 71 |

## *Appendix 3.2.3. Embase*

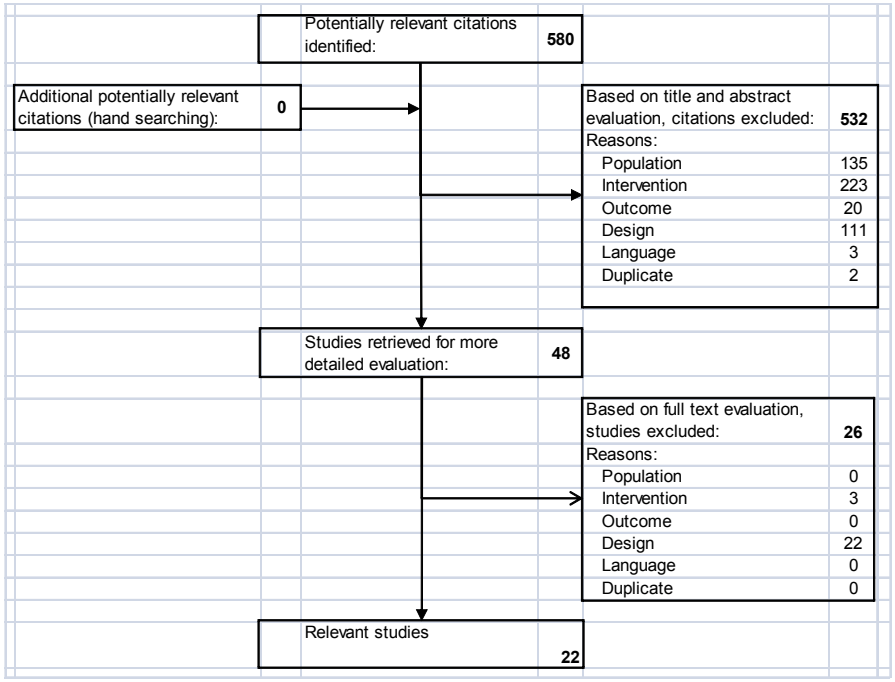
**Emtree terms :**

- prostate cancer, castration resistant prostate cancer, prostate adenocarcinoma, prostate carcinoma, prostatic intraepithelial neoplasia, (This term was added to Emtree in 1974),Synonyms : cancer, prostate; prostate gland cancer; prostatic cancer
- “watchful waiting” . This term was added to Emtree in 2007
- Active surveillance: no emtree term, free text
- Prostatectomy: This term was added to Emtree in 1974, Synonyms:prostate adenectomy; prostate resection; prostatic adenectomy; radical prostatectomy; total prostatectomy. **Dorland's dictionary:** prostatectomy = surgical removal of the prostate or of a part of it.Radical prostatectomy = removal of the prostate with its capsule, seminal vesicles, ductus deferens, some pelvic fasciae, and sometimes pelvic lymph nodes; performed via either the retropubic or the perineal route.

- Radiotherapy . Ths term was added to Emtree in 1974. Synonyms : bioradiant therapy; bucky irradiation; bucky radiation; bucky radiotherapy; bucky ray; bucky ray radiation; bucky therapy; fractionated radiotherapy; hemibody irradiation; hypophysectomy, radiation; hypophysis irradiation; hypophysis radiation; irradiation therapy; irradiation treatment; irradiation, hypophysis; lymphatic irradiation; pituitary irradiation; radiation beam centration; radiation repair; radiation therapy; radiation treatment; radio therapy; radio treatment; radiohypophysectomy; radiology, therapeutic; radiotreatment; roentgen irradiation, therapeutic; roentgen therapy; roentgen treatment; therapeutic radiology; therapy, irradiation; therapy, radiation; therapy, roentgen; treatment, irradiation; treatment, radiation; treatment, roentgen; x-ray therapy; x radiotherapy; x ray therapy; x ray treatment. Emtree Scope Note radiotherapy = Used as a disease subheading for the treatment of a disease using radiotherapy
- (Neo)adjuvant therapy. This term was added to Emtree in 1974. Synonyms : adjuvant effect; adjuvant treatment; neoadjuvant therapy; radiotherapy, adjuvant. **Dorland's dictionary** : neoadjuvant therapy = in combined modality therapy for cancer, initial use of one modality, such as chemotherapy or radiotherapy, to decrease the tumour burden prior to treatment by another modality, usually surgery. Called also preoperative t. and presurgical t.
- adjuvant therapy = the use of chemotherapy or radiotherapy in addition to surgical resection in the treatment of cancer.
- Androgen antagonist . This term was added to Emtree in 1974. Synonyms : androgen antagonist; androgen antagonists; anti androgen; antiandrogen agent; antiandrogenic agent; antiandrogenic drug; nonsteroidal anti-androgen; nonsteroidal anti-androgens; nonsteroidal anti androgen; nonsteroidal anti androgens; nonsteroidal antiandrogen; nonsteroidal antiandrogens. **Dorland's dictionary** : antiandrogen = any substance capable of inhibiting the biological effects of androgens.

| | |
|---|---|
| **Date** | From 2007 until 01/2011 |
| **Database** | Embase |
| **Search Strategy (Emtree terms, see below)** | 'prostate cancer'/exp AND 'watchful waiting'/exp AND (watchful AND waiting OR observation OR expectant AND management OR careful AND monitoring OR surveillance OR delay OR (deferred AND treatment OR no AND initial AND treatment)) AND ('prostatectomy'/exp OR 'radiotherapy'/exp OR 'antiandrogen'/exp OR 'adjuvant therapy'/exp) AND [embase]/lim AND [2007-2012]/pyAND 'clinical trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'human'/de OR 'prospective study'/de OR 'randomized controlled trial'/de) |
| **Note** | 55 (16 duplicates with Medline) |

### *Appendix 3.2.4. Results*




The quality of the retrieved SR, M-A and RCT was assessed using the checklists of the Dutch Cochrane Centre (www.cochrane.nl). All critical appraisals were done by a single KCE expert.

From those 22 relevant studies, 9 were included after critical appraisal (see point 4.1 and 4.2) and 13 not (see point 4.3)

## Appendix 3.3. Randomised control trials for question 3

P:localized prostate cancer

I: protocol X for active surveillance

C: protocol Y for active surveillance

O: mortality, morbidity, quality of life

### *Appendix 3.3.1. Medline*

| | | |
|---|---|---|
| **Project number** | 2011-01-GCP | |
| **Project name** | Prostate cancer /active surveillance strategies | |
| **Search question(s)** | Did different active surveillance strategies affect the outcomes? (question 4.3.1) | |
| **Structured search question(s) (PICO, SPICE, ECLIPSE, ..)** | | and related keywords |
| **P (patient)** | Low risk prostate cancer | Prostatic Neoplasms |
| **I (Intervention)** | Protocol1 | Active surveillance |
| **C (comparison)** | Protocol2 | |
| **O (outcome)** | mortality | |
| **Date** | 09/08/2012 | |
| **Database** | Database: Ovid MEDLINE(R) < 2008 to August Week 1 2012> | |
| **Search Strategy** | 1 exp Prostatic Neoplasms/ (20765)<br>2 Prostatic Intraepithelial Neoplasia/ (279)<br>3 (prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.<br>(21304)<br>4 PIN.tw. (1811) | |

5 1 or 2 or 3 or 4 (26441)
6 watchful wait$.tw. (370)
7 (watch$ adj2 wait$).tw. (494)
8 watchful observation.tw. (5)
9 watchful surveillance.tw. (2)
10 watchful monitoring.tw. (6)
11 active surveillance.tw. (1136)
12 active monitoring.tw. (63)
13 expectant manag$.tw. (350)
14 expectant monitoring.tw. (13)
15 expectant surveillance.tw. (1)
16 deferred treatment$.tw. (23)
17 deffered therap$.tw. (0)
18 delayed treatment$.tw. (440)
19 delayed therap$.tw. (60)
20 conservative monitoring.tw. (2)
21 conservative surveillance.tw. (1)
22 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (2509)
23 5 and 22 (508)
24 limit 23 to yr="2011 -Current" 38

### *Appendix 3.3.2. Cochrane*

| | |
|---|---|
| **Date** | From 2008 until 09/08/2012 |
| **Database** | CDSR, CCRCT |
| **Search Strategy (MESH term)** | Prostatic Neoplasms/th |
| **Result** | After exclusion of articles non relevant for this question : no |

### *Appendix 3.3.3. Embase*

| | |
|---|---|
| **Date** | From 2008 until 10/08/2012 |
| **Database** | Embase |
| **Search Strategy (Emtree terms, see below)** | 'prostate cancer'/exp/mj OR 'prostate cancer' AND active AND surveillance AND [controlled clinical trial]/lim AND [english]/lim AND [2011-2013]/py |
| **Result** | 7 |

Forty four potentially relevant citations were identified.

After reviewing the 11 publications selected, no studies comparing different active surveillance strategies was found.

# APPENDIX 4. QUALITY APPRAISAL

## Appendix 4.1. Guidelines

**Table 5 – Guidelines apraisal followig AGREE tool**

| | NICE | AUA | EAU | VIKC-CBO | ARAGON |
|---|---|---|---|---|---|
| **Domain 1. Scope and Purpose** | | | | | |
| 1. overall objective | 6,5 | 7,0 | 6,0 | 7,0 | 6,5 |
| 2. health question(s) | 6,5 | 6,5 | 6,0 | 7,0 | 7,0 |
| 3. population | 7,0 | 7,0 | 6,0 | 6,5 | 7,0 |
| **Domain score** | **94,4** | ***97,2*** | ***83,3*** | ***97,2*** | ***100,0*** |
| **Domain 2. Stakeholder Involvement** | | | | | |
| 4. all relevant professional groups | 6,5 | 6,5 | 5,0 | 6,0 | 4,5 |
| 5. target population views and preferences | 6,0 | 1,0 | 1,0 | 3,5 | 1,0 |
| 6. target users | 7,0 | 6,0 | 6,5 | 7,0 | 4,0 |
| **Domain score** | **91,7** | ***58,3*** | ***52,8*** | ***75,0*** | ***50,0*** |
| **Domain 3. Rigour of Development** | | | | | |
| 7. systematic search | 7,0 | 7,0 | 6,0 | 4,5 | 6,0 |
| 8. selection criteria | 6,0 | 6,5 | 3,5 | 5,0 | 4,0 |
| 9. strengths and limitations of evidence | 5,0 | 6,5 | 5,5 | 4,0 | 4,5 |
| 10. formulation of recommendations | 6,0 | 6,0 | 5,0 | 6,0 | 4,0 |
| 11. benefits, side effects and risks | 6,0 | 6,0 | 5,0 | 5,5 | 2,5 |
| 12. explicit link | 6,5 | 6,0 | 7,0 | 6,5 | 4,0 |
| 13. external review | 5,5 | 5,0 | 1,0 | 5,0 | 5,0 |
| 14. update procedure | 6,5 | 5,5 | 5,5 | 6,0 | 6,5 |
| **Domain score** | **84,4** | ***84,4*** | ***56,3*** | ***67,7*** | ***70,8*** |
| **Domain 4. Clarity of Presentation** | | | | | |
| 15. specific and unambigious | 6,5 | 6,5 | 5,5 | 4,0 | 7,0 |
| 16. different options for management | 7,0 | 7,0 | 6,0 | 6,0 | 4,0 |
| 17. key recommendations | 7,0 | 7,0 | 5,5 | 7,0 | 6,5 |
| **Domain score** | **97,2** | ***97,2*** | ***77,8*** | ***77,8*** | ***100,0*** |
| **Domain 5. Applicability** | | | | | |
| 18. facilitators and barriers | 5,0 | 1,0 | 1,0 | 7,0 | 1,5 |
| 19. advice and tools | 5,0 | 3,0 | 1,0 | 6,5 | 6,0 |
| 20. possible resource implications | 1,0 | 1,0 | 1,0 | 1,0 | 1,0 |
| 21. monitoring and/or auditing criteria | 4,0 | 1,0 | 1,0 | 6,0 | 1,0 |
| **Domain score** | **45,8** | ***8,3*** | ***0,0*** | ***68,8*** | ***25,0*** |
| **Domain 6. Editorial Independence** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 22. editorially independent | 6,5 | 6,5 | 6,5 | 6,5 | 6,5 |
| 23. conflicts of interest | 7,0 | 6,5 | 6,5 | 6,5 | 7,0 |
| **Domain score** | **95,8** | ***91,7*** | ***91,7*** | ***91,7*** | ***100,0*** |
| **Number of items scoring ≥ 5** | **21** | **18** | **16** | **18** | **11** |
| **Number of domains scoring > 60%** | **5** | **4** | **3** | **6** | **4** |

Finally, we selected three guidelines[8-10] of high quality and two[11, 26] of moderate quality according to AGREE score.

## Appendix 4.2. Systematic Reviews

| Items | AHRQ | Farmaka | Hegarty | Wilt-SR |
|---|---|---|---|---|
| **Search date** | August 2011 | August 2010 | July 2010 | September 2007 |
| **Inter-vention** | Curative Treatment | Radical Prostatectomy (RP) | Curative treatment | Any prostate cancer treatment |
| **Control** | AS | WW/AS | WW | Any prostate cancer treatment |
| **1** | Yes | Yes | Yes | Yes |
| **2** | No : restricted | Yes/No | Yes | Yes |
| **3** | ? | ? | Yes | Yes |
| **4** | Yes/No | Yes/No | Yes | Yes |
| **5** | Yes | Yes | Yes | Yes |
| **6** | Yes | Yes | Yes | Yes |
| **7** | NA | NA | NA | NA |
| **8** | NA | NA | NA | NA |
| **9** | Yes | Yes | Yes | Yes |
| **Quality** | Moderate | Moderate | High | High |

*Legend of items 1 to 9 of the quality appraisal:*
*1. Is de vraagstelling adequaat geformuleerd?*
*2. Is de zoekactie adequaat uitgevoerd?*
*3. Is de selectieprocedure van artikelen adequaat uitgevoerd?*
*4. Is de kwaliteitsbeoordeling adequaat uitgevoerd?*
*5. Is adequaat beschreven hoe data-extractie heeft plaatsgevonden?*
*6. Zijn de belangrijkste kenmerken van de oorspronkelijke onderzoeken beschreven?*
*7. Is adequaat omgegaan met klinische en statistische heterogeniteit van de onderzoeken ?*
*8. Is statistische pooling op een correcte manier uitgevoerd ?*
*9. Zijn de resultaten van de systematische review valide en toepasbaar?*

## Appendix 4.3. Randomised Controlled Trials

| Items | Bill-Axelson | Iversen | Fransson | Johansson | Wilt-PIVOT |
|---|---|---|---|---|---|
| **Intervention** | RP | RP + oral placebo | Radiotherapy | RP | RP |
| **Control** | WW | oral placebo alone | WW | WW | Observation |
| **1** | Yes | Yes | ? | Yes | Yes |
| **2** | Yes | ? | ? | Yes | ? |
| **3** | No | No | ? | No | No (not possible) |
| **4** | No | No | ? | No | No (not possible) |
| **5** | Yes | ? | ? | Yes | ? |
| **6** | Yes | No | Yes | No | Yes |
| **6 bis** | | No | | ? | |
| **7** | Yes | No | ? | ? | Yes |
| **7 bis** | | No | | ? | |
| **8** | Yes | Yes | Yes | Yes | Yes |
| **9** | Yes | Yes | | Yes | Yes |
| **10** | Non car le cancer de la prostate est détecté par le dosage de PSA actuellement, ce qui n'est pas le cas dans cette RCT. | Douteux car de nombreuses questions méthodologiques entachent les résultats : pouvoir statistique, exclusion de l'analyse de 22% des hommes de l'échantillon initial, différence d'âge entre les 2 groupes, diagnostic sans bone scan. | Douteux. Trop peu d'information dans cet article pour répondre à cette question. | Non, les résultats sont peu applicables au vu du mode de diagnostic (non basé sur le dosage de PSA) et de la chirurgie peu conservative pratiquée. | Oui, beaucoup plus proche de la situation nationale car ¾ de la population a été diagnostiquée à la suite d'un PSA élevé. |
| **Quality** | High | Poor | poor | High | high |

*1. L'attribution de l'intervention aux patients a-t-elle été réalisée de manière aléatoire (randomisation)?*
*2. Celui qui inclut les patients ignore l'ordre de succession aléatoire. Est-ce le cas?*
*3. Le traitement était-il étudié en aveugle pour le patient?*
*4. Le traitement était-il réalisé en aveugle pour les soignants?*
*5. Le traitement était-il réalisé en aveugle pour ceux qui évaluent les résultats ?*
*6. Les groupes étaient-ils comparables au début de l'étude ?*
*6 bis. Si non, cela a-t-il été corrigé lors de l'analyse des résultats ?*
*7. Parmi les patients inclus, une proportion suffisante a-t-elle disposé d'un suivi complet ?*
*7 bis. Si non : une perte sélective de patients lors du suivi est-elle exclue?*
*8. Tous les patients inclus ont-ils été analysés dans les groupes dans lesquels ils ont été randomisés ?*
*9. En dehors de l'intervention, les groupes sont-ils traités de façon semblable ?*
*10. Le résultat obtenu peut-il être appliqué à la situation nationale ?*

# APPENDIX 5. DATA EXTRACTION TABLES

## Appendix 5.1. Systematic reviews

All systematic reviews included the same two controls trials: the SPCG-4 trial (good quality) (see Bill-Axelson point 5.2.1) and the VACURG (poor quality) (see Iversen point 5.2.1).

| I Study ID | II Method | III Patient characteristics | IV Intervention(s) | V Results primary outcome | VI Results secondary and other outcome(s) | VII Critical appraisal of review quality |
|---|---|---|---|---|---|---|
| **AHRQ. "An Evidence Review of Active Surveillance in Men With Localized Prostate Cancer"**<br><br>**2011** | Systematic review to summarize the existing literature regarding the role of AS in the management of early-stage, low-risk prostate cancer<br>(1 subquestion is comparative effectiveness of AS vs active treatments).<br>Funding : National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR)<br>Search date: August 2011<br>Database: Medline (OVID), CDSR, specific database (epidemiology, economic) et experts<br>Study designs : RCT & non randomize comparative studies of treatments, multivariable association studies, & studies of temporal trends in prostate cancer natural history. Only published, peer-reviewed, English-language articles were selected based on predetermined eligibility | Men with clinically localized prostate cancer (T1-T2), without known lymph nodes (N0-X) or metastases (M0-X) | Radical prostatectomy (RP) or external beam radiation therapy (RT) or brachytherapy (alone or combined), with or without ADT.<br><br>Active surveillance (AS) = In fact, there was no standardized definition of active surveillance. Sixteen cohorts used different monitoring protocols, all with different combinations of periodic digital rectal examination, PSA testing, rebiopsy, and/or imaging findings. Predictors that a patient received no initial active treatment generally included older age, presence of comorbidities, lower Gleason score, lower tumour stage, lower diagnostic PSA, and lower disease progression risk group. | No trial provided results comparing men with localized disease on active surveillance with surgery or radiation therapy.<br>Therefore, there is insufficient evidence for the comparative short- and long-term outcomes of AS versus immediate definitive treatment for localized prostate cancer.<br>For other observational management strategies (largely resembling WW), in addition to previously published systematic reviews and evidence reports, 2 updates from multicenter RCTs and 16 cohort studies (3 prospective and 13 retrospective) were selected.<br>- lower all-cause or prostate cancer-specific mortality rates with RP vs WW; SPCG4 (sse Bill-Axelson point 4.2.1) trial found significantly lower incidences of all-cause deaths (24 vs. 30 percent),disease-specific deaths (10 vs. 15 percent), | - less risk of urethral stricture with observational strategy vs RP;<br>- higher short and long term cost for RP or RT vs WW. | Moderate<br><br>The literature search focused on Medline & CDSR only and it's no clear if the quality appraisal of the primary studies was taken into account.<br><br>The majority of evidence for this Key Question came from retrospective analyses of observational studies. Confounding by indication is likely in these studies, due to the differences in patient characteristics and risk profile between patients treated with observational strategies and those who received active treatment.<br>No pooling was done |

| | | | | | | |
|---|---|---|---|---|---|---|
| | criteria<br>No trial found for the sub question about the effectiveness of AS but 2 updates RCT, 16 cohort studies for other observational management strategies (largely resembling WW), 4 reports and 2 cost modelin | | | | | |
| **Farmaka**<br>**Le traitement efficient des pathologies prostatiques bénignes et malignes**<br>**2011** | Systematic review to:<br>- prepare a consensus conference about the "traitement effi cient des pathologies bénignes et malignes de la prostate"<br>- a subquestion of this search was : "Dans quels cas (criteres precis) une attitude de surveillance active peut-elle etre justifiee pour un cancer de la prostate ?"<br>Funding : National Sickness Fund<br>Search date: August 2010<br>Database: MEDLINE, Cochrane Library & Dare.<br>Study designs : 1 RCT & 7 Observational study.Three ongoing studies were cited . | Men with prostate cancer (no other precision) | Radical prostatectomy<br>WW= to avoid treatment; palliative intent<br>AS= to individualize treatment; curative intent | There are currently no published RCT on active surveillance (only on watchfull waiting).<br>In the RCT on WW (SPCG-4,sse Bill-Axelson point 4.2.1)), WW is associated with a slight specific mortality rate and a reduced local and metastatic progression.<br>In the 7 cohort studies (with a maximum follow-up of 7 years), AS in men with early stage PCa is associated with slight specific (> 3% at max 13 years of follow-up) mortality rates.<br>The exact place of AS, the type of patients who get the greatest benefit of this approach and the monitoring protocol are to be defined. | | Moderate<br>ADAPTE methodology<br>No pooling was done |
| **Hegarty J. & al: "Radical prostatectomy versus watchful waiting for prostate** | Systematic review to:<br>- compare the beneficial and harmful effects of RP versus WW for the treatment of clinically localised prostate cancer<br>- test the null hypothesis of no difference in terms of the primary, secondary | Men with clinically localized prostate cancer = confirmed prostate cancer (as verified by cytological | Radical prostatectomy (RP) = removal of the entire prostate gland and some surrounding tissue performed by any method (e.g. retropubic, perineal, laser, robotic or laparoscopic) with or without nerve sparing | All cause mortality after 23 years (VACURG):<br>10.6 years for RP vs 8 years for WW (p>0.05) (but poor methodological quality of the trial)<br>All cause mortality after 15 years (VACURG):<br>Hazard Ratio (HR) = 0.9 (0.56 | Distant metastases after 12 years (SPCG-4) :<br>19.3% vs 26%<br>RD = -6.7% (-13.2 to -0.2);<br>RR = 0.65 (0.47 to 0.88); p=0.006<br>Incidence of local recurrence and/or progression after 12 | High<br>None RCT enrolled men with primarily PSA-detected disease (only 5.2% in SPCG-4)<br>Not applicable to men with significant co-morbidities (enrollment of men < 75 years with a LE of 10 years in SPCG-4) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **cancer (Review)"**<br><br>**2010** | and tertiary outcomes between RP and WW<br>Funding : Health Research Board, Ireland<br>Search date: 30 July 2010<br>Database: MEDLINE, EMBASE, The Cochrane Library, ISI Science Citation Index, DARE, LILACS.<br>Study designs : RCT or quasi-RT | or histological examination) which is believed to be still confined to the prostate gland (T0 or T1 or T2). | procedures, with or without sampling of the pelvic lymph nodes.<br><br>Watchful waiting (WW) = any conservative approach whereby a decision is made to provide no initial treatment and to monitor the patient. Palliative treatment can offer if evidence of disease progression. | to 1.43).<br>All cause mortality after 12 years (SPCG-4):<br>32.7% vs 39.8%<br>RD = -7.1% (-14.7 to 0.5);<br>RR = 0.82 (0.65 to 1.03); p=0.09<br>Prostate cancer mortality after 12 years SPCG4 (sse Bill-Axelson point 4.2.1)<br>12.5% vs 17.9%<br>RD = -5.4% (-11.1 to 0.2);<br>RR = 0.65 (0.45-0.94); p=0.03<br><br>Thus, RP is likely to reduce the risks of overall mortality, prostate-cancer mortality and distant metastases compared to WW, but the magnitude of the effect is unclear (width of CI) and the risk reductions appear to have been limited to men less than 65 years of age. | year (SPCG-4): 21.7% vs 45.6%)<br>RD = -23.9% (-30.9 to -16.8);<br>RR = 0.36 (0.27 to 0.47); p< 0.001<br>Erectile dysfunction after 4 years (SPCG-4): 80% vs 45%<br>RD = 35% (25 to 45)<br>RR = 1.78 (1.48 to 2.15)<br>Urinary leakage after 4 years (SPCG-4): 48.7% vs 21.3%<br>RD = 27% (17 to 37)<br>RR = 2.29 (1.63 to 3.22)<br>Urinary obstruction after 4 years (SPCG-4): 34.5% vs 49.3%<br>RD = -15% (-26 to -4)<br>Bowel symptoms after 4 years (SPCG-4): no ss difference<br>Psychological function after 4 years (SPCG-4): no ss difference | Difference between WW and active surveillance (where patient are monitored closely and where appropriate treatment is promptly initiated)<br>RP appears to increase the risks of erectile dysfunction and urinary leakage but confident statements cannot be made about how frequently these adverse effects occur. Furthermore these estimates must be interpreted cautiously as they are derived from data obtained from a self-administered questionnaire survey of a sample of the trial participants (N = 326), within no baseline quality of life data were obtained and nerve-sparing surgery was not routinely performed on trial participants undergoing RP.<br>No pooling was done |
| **Wilt T.J. & al. "Systematic Review: Comparative Effectiveness and Harms of**<br><br>**Treatments for Clinically Localized Prostate Cancer"** | Systematic review to determine:<br>- the comparative short- & long-term benefits and harms of therapies for clinically localized prostate cancer<br>- how patients and tumour characteristics affect the outcomes of these therapies.<br>Funding : AHRQ<br>Search date: Mi-Sept 2007<br>Database:<br>- For RCT : Cochrane | Men with clinically localized prostate cancer (T1 or T2) | Any prostate cancer treatment<br>vs<br>Any prostate cancer treatment | For RP vs WW:<br>Overall survival (VACURG) = 10.6 years for RP vs 8 years for WW (p>0.05) (but underpowered study).<br>All cause mortality after 10 years (SPCG-4) :<br>RD = 5% (-2.8 to 13.0)<br>Prostate cancer mortality after 10 years (SPCG-4):<br>10% vs 15% (p=0.01) | Distant metastases after 10 years (SPCG-4) :<br>15.2% vs 25.4%;<br>RD = 10.2% (3.1 to 17.2)<br>Sexual dysfunction (SPCG-4):<br>RR = 1.2 to 18.0 for specific domains<br>Overall distress from all urinary symptoms (SPCG-4):<br>27% vs 18% ; | High<br>Effectiveness of RP vs WW for overall and disease-specific survival but may be limited to men < 65 y.<br>Increase risk of sexual and urinary dysfunction with RP vs WW ; worse bowel symptom after WW vs RP.<br>Assessment of the comparative effectiveness and harms of localized prostate cancer treatments difficult because of limitations in the evidence. |

| | | | | |
|---|---|---|---|---|
| **2008** | library, Cochrane Review Group in Prostate Diseases and Urologic malignancies specialized registry (Nov 2007);<br><br>- For observational studies (to demonstrate the range of specific outcomes) : PubMed (1991-2004 without update).<br><br>- For long-term HRQoL: Prostate Cancer Outcomes Study (PCOS)<br><br>- For outcomes with emerging therapy : Medline (April 2004- Sept 2007) & contact with Endocare<br><br>- For Effect of patient and tumour characteristics: reviewing RCT, AUA database and U.S. population-based observational studies<br><br>Included studies:<br><br>For RP vs. WW: 2 RCT<br><br>1. SPCG-4 : Bill-Axelson et al., 2005 (sse Bill-Axelson point 4.2.1) (good quality)<br><br>2. VACURG: (poor quality) (see Iversen, point 4.2.1) | | RR = 1.5 (1.0 to 2.3)<br><br>Distress from all bowel symptoms (SPCG-4): 3% vs 6%<br><br>Inability to attain an erection (PCOS): 86% if AD, 58% if RP vs 33% in WW.<br><br>Patient satisfaction (PCOS): higher with early intervention vs WW. | None RCT enrolled men with primarily PSA-detected disease |

# Appendix 5.2. Primary Studies For Treatment

## *Appendix 5.2.1. RCT : Mortality-morbidity*

| I Study ID | II Method | III Patient characteristics | IV Intervention(s) | V Results primary outcome | VI Results secondary and other outcome(s) | VII Critical appraisal of study quality |
|---|---|---|---|---|---|---|
| **Bill-Axelson et al. "Radical prostatectomy versus Watchful waiting in early prostate cancer"**<br><br>**2011**<br><br>**(+ Homberg 2002 for design)** | • RCT SPCG-4<br>• Funding: Swedish Cancer Society & National Institutes of Health<br>• Setting:14 centers in Sweden, Finland & Iceland<br>• Sample size: 695<br>• Recruitment duration: Oct 1989- Feb 1999<br>• Follow-up: 15 years | • Newly diagnosed, localized prostate cancer T0d,T1,T2 (1978 criteria).<br>• Tumour well or moderately well differenciated<br>• Predominantly detected by symptoms, rather than PSA.<br>• Life expectancy >10 years<br>• < 75 years old.<br>• No other known cancers<br>• Serum PSA level < 50 ng/ml.<br>• < 25% of the tumour = Gleason 4 & < 5%= Gleason 5.<br>• No sign of obstruction of the upper urinary tract.<br>• Negative bone scan<br><br>Comparable groups with the exception of a somewhat higher proportion of men with stage T1b tumours in the WW group; but most of the men had stage T2 tumours. | **RP** (n=347)<br><br>= pelvic lymph node evacuation and Walsh-Lepor radical prostatectomy if no nodal metastases found<br><br>• hormonal therapy if local recurrence (orchidectomy or gonadotropin-releasing hormones analogues)<br><br>• hormonal therapy if metastases detected by bone scan or, after 2003, if signs of tumour progression, including elevations of PSA level.<br><br>**WW** (n=348)<br><br>= no initial treatment (except TURP already done) :<br><br>• transurethral resection if signs of obstructive voiding disorders<br>• hormonal therapy if metastases detected by bone scan or, after 2003, if signs of tumour progression, including elevations of PSA level.<br><br>Follow-up every 6 month (clinical examination and blood test thereafter) for the | • All cause death :<br>Absolute risk reduction (ARR)=6.6 (-1.3 to 14.5)<br>RR=0.75 (0.61 to 0.92)<br>P=0.007<br>NNT=15<br><br>but for men < 65 years:<br>ARR= 13.5 (2.4 to 24.7)<br>RR=0.52 (0.37 to 0.73)<br>P< 0.001<br>NNT=7<br><br>• Prostate cancer death :<br>ARR=6.1 (0.2-12.0)<br>RR=0.62 (0.44-0.87)<br>P=0.01 | • Distant metastases:<br>ARR=11.7 (4.8 to 18.6)<br>RR=0.59 (0.45 to 0.79)<br>P < 0.001<br><br>• Local progression :<br>ARR=27.9 (20.9 to 34.8)<br>RR=0.34 (0.26 to 0.45)<br><br>• Post-operative complications after RP:<br>Impotence= 58.1% (52.7 to 64.1)<br>Urinary leakage=32.2%(27.2 to 38.1) | • No patients lost to follow-up until December 31, 2009<br><br>• Critical appraisal: High<br><br>But<br><br>• Trial initiated before the era of screening by PSA.<br><br>• Radical nature of surgery rather preservation of potency.<br><br>• Population < 75 years with >10 LE (not representative of general population)<br><br>• WW = not Active surveillance (where patients are monitored closely and promptly treated if signs of progression) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | first 2 years, then annually (+bone scan and chest x-ray annually before 2003, bone scan every 2 years after) | | | |
| **Iversen et al. "Radical prostatectomy versus Expectant treatment for early carcinoma of the prostate"**<br><br>**1995** | • RCT VACURG<br>• Funding: ?<br>• Setting : 15 Veterans Administration Hospitals in U.S.<br>• Sample size: 111/142<br>• Recruitment duration: May 1967-March 1975<br>• Follow-up: 15 y | • Newly diagnosed, histologically confirmed adenocarcinoma of the prostate<br>• Stage I and II (Gleason)<br>• Previously untreated<br><br>Comparable group a part for mean age (62.7 years in RP vs 66.0 years in EP) | **RP**<br><br>= retropubic radical prostatectomy + oral placebo<br><br>Without prior pelvic lymphadenectomy<br><br>**Expectant Treatment (ET)**<br><br>= oral placebo alone<br><br>Follow-up every 6 month (no bone scan!) until 1978, no regular FU after because of a lack of funding. | • Overall survival:<br><br>10.6 vs 8 years (NSS) | | • No patients lost to follow-up<br>• Critical appraisal: Low<br>• Trial initiated before the era of screening by PSA<br>• Possible enrollment of patients with disseminated disease because of lack of bone scan and diagnostic lymphadenectomy in routine evaluation.<br>• Small sample size<br>• Drop out (31) |
| **Wilt et al .**<br><br>**"Radical Prostatectomy versus Observation for Localized Prostate Cancer"**<br><br>**2012** | • RCT : PIVOT<br>• Funding : Dpt of Veterans Affairs, National Cancer institute and AHRQ<br>• Setting : 44 Department of Veterans Affairs sites and 8 National Cancer Institute sites.<br>• Sample size : 731 (364+367)<br>• Recruitment duration : Nov 1994-Jan2002 | • Histologically confirmed, clinically localized prostate cancer (stage T1-T2NxM0 of any grade) diagnosed within the previous 12 months<br>• The mean age was 67 years. 1/3 of the patients<br>• were black; 85% reported full independence in<br>• activities of daily living. The median PSA value was<br>• 7.8 ng per milliliter (mean, 10.1). About 50% of the men had stage T1c disease (not palpable, detected by means of PSA testing), and | • RP:technique was let at the surgeon's discretion<br>• Observation ; Men were offered palliative therapy or chemotherapyfor symptomatic or metastatic progression.<br>• Follow-up : every 6 months for a minimum of 8 years and a maximum of 15 years or until the patient died. Bone scans were obtained at 5, 10, and 15 years or at the last visit for persons with less than 15 years of follow-up with additional scans obtained at the | • All-cause mortality :<br>• Among the entire group (HR:, 0.88; 95% confidence interval [CI], 0.71 to 1.08; P = 0.22; absolute risk reduction, 2.9 percentage points; 95% CI, −4.1 to 10.3 in favour of RP).<br>• The absolute reduction in mortality with radical prostatectomy was not significant at any interval and declined over time, from 4.6 | Prostate cancer mortality :<br>• Among the entire group (hazard ratio, 0.63; 95% CI, 0.36 to 1.09; P = 0.09; absolute risk reduction, 2.6 percentage points; 95% CI, −1.1 to 6.5)<br>• Among men with PSA< 10 ng/ml : (hazard ratio, 1.03; 95% CI, 0.79 to 1.35).<br>• Among men with PSA > 10 ng/ml : (hazard ratio, 0.67; 95% CI,0.48 to 0.94)<br>• Among men with low risk tumour : (hazard ratio, 1.15; 95% CI, 0.80 to 1.66).<br>• Among men with | • No patients lost to follow-up<br>• Intention to treat analysis<br>• About 50% of the men had disease (not palpable, detected by means of PSA testing.<br>• Critical appraisal : high |

| | | | | | | |
|---|---|---|---|---|---|---|
| | • Median follow-up : 10 years | about 25% had histologic scores of 7 or higher on the Gleason scale; 40% of the men had low-risk, 34% intermediate-risk, and 21% high-risk prostate cancer<br>• Randomization process was designed to create comparable treatment groups | clinician's discretion. | percentage points (95% CI, −0.2 to 9.3) at 4 years to 2.9 percentage points (95% CI, −4.2 to 10.0) at 12 years. | intermediate risk tumour : (hazard ratio, 0.69; 95% CI,0.49 to 0.98; absolute risk reduction, 12.6 percentage points)<br>• Among men with high risk tumour:: nonsignificant absolute reduction in mortality of 6.7 percentage points, as compared with observation (P = 0.16) | |

## *Appendix 5.2.2. Quality of life*

| I Study ID | II Method | III Patient characteristics | IV Intervention(s) | VI Results secondary and other outcome(s) | VII Critical appraisal of study quality |
|---|---|---|---|---|---|
| **Fransson P, et al. Health-related quality of life 10 years after external beam radiotherapy or watchful waiting in patients with localized prostate cancer**<br><br>**2009** | • RCT<br>• Funding: Swedish Cancer Society (Unmea Trial 1 Study)<br>• Setting:?<br>• Sample size: 54/72<br>• Recruitment during 1986-1996<br>• Begin of this follow-up in 2004<br>• Follow-up: 4 and 10 years<br><br>According to the authors, the UMEA1 trial is not yet ready for publication!<br><br>2 questionnaires:<br>• PCSS (updated version of the validated QUFW94 formula)<br>• EORTC QLQ-C30 | • Localized prostate cancer.<br>• No previous treatment<br>• No other disease with an expected survival time < normal population of the same age<br><br>Group comparability: ? (appears OK for age but for PSA?) | **RT** (n=27)<br><br>5 fractions/week with daily dose of 2.0 Gy.(change in protocol in 1993 from four-field small-box technique to four-field conformal radiation therapy)<br><br>**WW** (n=27)<br><br>= monitoring regularly and treatment deferred until progression. | • HRQol : no statistically significant differences (symptom scale; limitation in daily life; life situation) and few change over time from 4 to 10 year<br><br>• Symptom evaluation :<br>o Urinary bother : no difference a part weak urinary stream (mean 4.8 vs 3.0; p=0.034)<br>o Bowel symptoms : no difference<br>o Sexual bother : more after RT (mean : 7.4 vs 3.8, p=0.011) but no difference in erectile function, nor in maintaining a sufficient erection to perform intercourse, nor in the HRQoL question) | • Decreasing number of questionnaires completed in the FU.<br>• Critical appraisal: Medium<br><br>Small sample size<br><br>Lack of baseline data because evaluating HRQoL was not the aim of the study protocol.<br><br>PCSS instrument validated but maybe difficult to interpret.<br><br>Quid about PSA detection or not? Quid about the kind of follow-up. |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Johansson E, Steineck G et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting.**<br><br>**2011** | • Longitudinal analysis from a RCT<br>• Funding: Swedish Cancer Society & National Institutes of Health<br>• Setting:14 centers in Sweden, Finland & Iceland<br>• Sample size: 400 living from SPCG-4; 349 answered once; 166 answered the questionnaire twice.<br>• Recruitment duration: Oct 1989- Feb 1999<br>• Questionnaires in 1997-1998 and between Oct 2006-Nov 2008<br>• Follow-up varied from 7 to 17 years (median 12.2)<br><br>Face-validated study-specific questionnaire<br><br>Questionnaire 1997-1998 : 77 items<br><br>Questionnaire 2006-2008: 141 items<br><br>Identical question about QoL and functional outcome in both questionnaires.<br><br>Additional information collected about potential confounders and effect-modifying factors (i.e concurrent diseases and treatments) | • 400 living Swedish and Finnish men from the 695 SPCG-4 population (Newly diagnosed, localized prostate cancer; Life expectancy >10 years; < 75 years old (cfr Bill-Axelson))<br><br>• 300 Swedish men from the Swedish Total Population Register, matched for region and age = compared group to understand the effect of leaving the prostate in place<br><br>Comparability of RP and WW but need of age adjusted calculation to offset the younger age of the compared group (because of a probable error in the age-interval machine). | **RP** (n=182 but 171 with really RP)<br><br>- hormonal therapy if local recurrence (19%)<br><br>**WW** (n=167)<br><br>- transurethral resection if signs of obstructive voiding disorders (15%)<br><br>- hormonal therapy if metastases detected by bone scan or, after 2003, if signs of tumour progression, including elevations of PSA level (28%).<br><br>**No intervention because no prostate cancer = controlled group (CG)** (n=214) | • Number of physical symptoms:<br>No difference RP-WW : 94% vs 94% reported 1 to 4 of erectile dysfunction, weak urinary stream, urinary leakage, or nocturia.<br>But 65% in the CG<br>• Erectile dysfunction (not exhaustive)<br>o 84% in RP, 80% in WW & 46% in CG.<br>o More men in distress due to erection in RP (48%) vs WW (36%) or CG (37%):<br>RR*=1.30 (1.00-1.70) RP vs WW<br>o More men in distress from lower self-esteem due to diminished erection in RP (39%) vs WW (23%) or CG (19%):<br>RR*=1.67 (1.20-2.33) RP vs WW<br>o Less frequency of orgasm (>1/last 6 months) in RP (18%) vs WW (26%) or Cg (58%):<br>RR*=0.62 (0.42-0.91) RP vs WW<br>• Urinary functions (not exhaustive)<br>o Less weak stream in RP (29%) vs WW (40%) :<br>RR*= 0.71 (0.53-0.96)<br>o Less nocturia in RP (49%) vs WW (63%):<br>RR*= 0.79 (0.65-0.95)<br>o More urinary leakage at least once daily in RP (41%) vs WW (11%) or CG (3%):<br>RR*= 3.79 (2.36-6.06) RP vs WW<br>o More night -time urinary leakage at least once a week in RP (20%) vs WW (8%) or CG (1%):<br>RR*= 2.58 (1.42-4.69) RP vs WW<br>o More feeling distress from urinary leakage in RP (18%) vs WW (9%) or CG (4%):<br>RR*= 2.08 (1.15-3.78) RP vs WW<br>o More regular dependence on some form of protective aid in RP (54%) vs WW (25%) or CG (8%):<br>RR*=2.15 (1.60-2.90) RP vs WW<br>• QoL<br>o Lower scores in all psychological measures if RP or WW vs CG but without significant result a part for anxiety.<br>o Moderate to high level of anxiety reported by the same proportion of patients in RP (43%) and WW (43%) but by fewer in the CG (33%): RR*=1.42 (1.07-1.88) | • Living and answering portion of the initial sample of SPCG-4.<br><br>• Critical appraisal: Medium<br><br>Diagnosis based on clinical symptom (not PSA detected).<br>Time to manifestation of erectile dysfunction or urinary disorder will be substantially longer for men diagnosed as a result of PSA screening.<br><br>RP more aggressive in the 1990s.<br><br>About ¼ of men from RP & WW group were AD; thus, perhaps with lower libido (and less acceptation of problem cfr Johansson 2008).<br><br>Absence of baseline data<br><br>Questionnaire validated in an unpublished pilot study and in other studies (?) |

*RR*= age adjusted risk relatif*

## Appendix 5.3. Publications Not Included

| | |
|---|---|
| Bill-Axelson A, et al. 2008 Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial | In Hegarty 2010 SPCG4 |
| Bill-Axelson A, et al.2005 Radical prostatectomy versus watchful waiting in early prostate cancer | In Hegarty 2010 SPCG4 |
| Dall'Era MA, et al. 2008 Active surveillance for low-risk prostate cancer: Selection of patients and predictors of progression | Review with a QA = 1 (only Medline, no information about QA of article, data extraction…)<br>Out after QA |
| Eggener SE, et al. 2007 Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. Review 50 refs | Nothing about watchful waiting or active surveillance<br>Out after text revision (subject) |
| Frattaroli J, 2008. Clinical events in prostate cancer lifestyle trial: results from two years of follow-up | Out after text revision (subject) |
| Holmberg L, et al. 2002 A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer | In Hegarty 2010 SPCG4 |
| Johansson E, et al. 2009 Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: | In Hegarty 2010 SPCG4 |
| Kasperzyk JL, et al. 2011 Watchful waiting and quality of life among prostate cancer survivors in the physicians' health study | Design: Cohort of physicians followed in a clinical trial for CV disease and cancer prevention! |
| Khatami A, et al. 2006 "PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section."<br>2007 | In Hegarty 2010,<br>Where it is not included because:<br>"This RCT does not randomise men to Radical Prostatectomy and an observation approach"<br>Out : scope (FU of group under surveillance to measure PSA doubling time. |
| Steineck G, et al. 2002 New England Journal of Medicine 347(11):790-6 - Quality of life after radical prostatectomy or watchful waiting | In Hegarty 2010 SPCG4 |
| Studer UE, et al. 2008 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) | Scope : PSA to guide timing of Androgen Deprivation; nor watchfull waiting or active surveillance vs AD not suitable for local curative treatment |
| Studer UE, et al. 2006 Journal of Clinical Oncology 24(12):1868-76 - 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 | Idem Studer 2008 |
| Thong MS, et al. 2009 Prostate cancer survivors who would be eligible for active surveillance but were either treated with radiotherapy or managed expectantly: comparisons on long-term quality of life and symptom burden | Design : cross-sectional (level of evidence 2c); 71 men, 10 years after low-risk localized prostate cancer managed with AS (systematic monitoring of men for whom curative treatment is deferred at diagnosis and who receive subsequent curative treatment when the tumour shows progression or when patients decide to change the treatment) were matched with 71 men managed by RT. |

| | |
|---|---|
| | Result : comparable HRQoL and lower symptom burden (bowel function, getting and maintening an erection) for AS vs RT, even after controlling for comorbidity and disease progress.<br>Out : desing : no RCT |
| van den Bergh RC, et al. 2010 Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? | Included in Hegarty 2010<br>Where it is not included because it is not a RCT<br>Design: evaluation of a prospective, single arm; observational protocol-based Active Surveillance program<br>Outcome : only biological tumour progression : gleason score, capsular penetration, tumour volume<br>Out : desing : no RCT |
| ProtecT trial | First results should be published after 2015 (http://www.epi.bris.ac.uk/protect/news/news.htm). |
| Start Trial | Unfortunately, this study was stopped early due to poor recruitment.No interim reports was published. |

# Appendix 5.4. Guidelines

## *Appendix 5.4.1. Patient point of view*

| Reference | Search date | Recommendations/conclusion | Level of evidence |
|---|---|---|---|
| **AUA 2007** | 2004 | Standard: A patient with clinically localized prostate cancer should be informed about the commonly accepted initial interventions including, at a minimum, active surveillance, radiotherapy (external beam and interstitial), and radical prostatectomy. A discussion of the estimates for benefits and harms of each intervention should be offered to the patient. | Panel consensus<br>Low |
| | | Standard: Patient preferences and health conditions related to urinary, sexual, and bowel function should be considered in decision making. Particular treatments have the potential to improve, to exacerbate or to have no effect on individual health conditions in these areas, making no one treatment modality preferable for all patients. | Panel consensus<br>Low |
| **VIKC 2007** | 2005 | Ter ondersteuning van de besluitvorming ten aanzien van de therapiekeuze moet de voorlichting aan patiënten met prostaatcarcinoom kwantitatieve gegevens bevatten over de resultaten en consequenties van de verschillende behandelmogelijkheden van de eigen kliniek. | Panel consensus<br>Low |
| | | Naast de behandelende arts speelt ook een gespecialiseerde verpleegkundige een belangrijke rol bij de voorlichting en begeleiding van mannen met prostaatcarcinoom. Het verdient aanbeveling in de status te vermelden wie de voorlichting heeft gegeven, welke behandelingsmogelijkheden zijn voorgesteld, en wat de te verwachten bijwerkingen zijn. | Panel consensus<br>Low |
| | | Bij de behandeling van patiënten met prostaatkanker is een gestructureerd, multidisciplinair overleg gewenst. | Panel consensus<br>Low |
| **NICE 2008** | Until June 2007 | Men with prostate cancer should be offered individualised information tailored to their own needs. This information should be given by a healthcare professional (for example, a consultant or specialist nurse) and may be supported by written and visual media (for example, slide sets or DVDs). | Low |
| | | Healthcare professionals caring for men with prostate cancer should ascertain the extent to which the man wishes to be involved in decision making and ensure that he has sufficient information to do so. | Low |
| | | A validated, up-to-date decision aid is recommended for use in all urological cancer multidisciplinary teams | high quality evidence and GDG |

| | | |
|---|---|---|
| | (MDTs). It should be offered to men with localised prostate cancer when making treatment decisions, by healthcare professionals trained in its use1 . | consensus. |
| | Healthcare professionals should adequately inform men with prostate cancer and their partners or carers about the effects of prostate cancer and the treatment options on their sexual function, physical appearance, continence and other aspects of masculinity. Healthcare professionals should support men and their partners or carers in making treatment decisions, taking into account the effects on quality of life as well as survival. | qualitative evidence and GDG consensus. |

## *Appendix 5.4.2. Risk Assessment*

| Reference | Search date | Recommendations/conclusion | Level of evidence |
|---|---|---|---|
| **AUA 2007** | 2004 | Standard: An assessment of the patient's life expectancy, overall health status, and tumour characteristics should be undertaken before any treatment decisions can be made. | Panel consensus<br>Low |
| **VIKC 2007** | 2005 | Bij iedere patiënt met verdenking op prostaatcarcinoom wordt de familie anamnese afgenomen. Als er op basis van de familieanamnese aanwijzingen zijn voor erfelijk prostaatcarcinoom dan wordt periodiek onderzoek verricht volgens de adviezen van de Stichting Opsporing ErfelijkeTumoren. | Panel consensus<br>Low |
| | | De Gleason score (inclusief de samenstellende componenten) wordt gebruikt bij de gradering van het prostaatcarcinoom en bij de beoordeling van prostaatnaaldbiopten. | Panel consensus<br>Low |
| **NICE 2008** | Until June 2007 | To help men decide whether to have a prostate biopsy, healthcare professionals should discuss with them their prostate specific antigen (PSA) level, digital rectal examination (DRE) findings (including an estimate of prostate size) and comorbidities, together with their risk factors (including increasing age and black African and Caribbean ethnicity) and any history of a previous negative prostate biopsy. The serum PSA level alone should not automatically lead to a prostate biopsy. | Low |
| | | Men and their partners or carers should be given information, support and adequate time to decide whether or not they wish to undergo prostate biopsy. The information should include an explanation of the risks (including the increased chance of having to live with the diagnosis of clinically insignificant prostate cancer) and benefits of prostate biopsy. | Well designed North American observational studies and GDG consensus<br>Low |
| | | Urological cancer multidisciplinary teams (MDTs) should assign a risk category to all newly diagnosed men with localised prostate cancer. | Low (cohort studies) |

## *Appendix 5.5.1. Treatment*

| Reference | Search date | Recommendations/conclusion | Level of evidence |
|---|---|---|---|
| **AUA 2007** | 2004 | Standard: A patient with clinically localized prostate cancer should be informed about the commonly accepted initial interventions including, at a minimum, active surveillance, radiotherapy (external beam and interstitial), and radical prostatectomy. A discussion of the estimates for benefits and harms of each intervention should be offered to the patient. | Panel consensus<br>Low |
| | | Option: Active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy are appropriate monotherapy treatment options for the patient with low-risk localized prostate cancer. | Panel consensus<br>Low |
| | | Standard: Patient preferences and health conditions related to urinary, sexual, and bowel function should be considered in decision making. Particular treatments have the potential to improve, to exacerbate or to have no effect on individual health onditions in these areas, making no one treatment modality preferable for all patients. | |
| | | Standard: When counseling patients regarding treatment options, physicians should consider the following:<br>Based on outcomes of one randomized controlled clinical trial, when watchful waiting and radical prostatectomy are compared, radical prostatectomy may be associated with a lower risk of cancer recurrence, cancer-related death, and improved survival. (based on SPCG4) | High |
| **VIKC 2007** | 2005 | Bij patiënten met een laag risico (T1c02a, Gleason< 7,PSA< 10 ng/mL) en een gevorderde leeftijd (>75jaar) verdient actief volgen de voorkeur. Daarbij legt men uit dat de levensverwachting niet wordt bepaald door het prostaatcarcinoom en dat elke behandeling een kans heeft op bijwerkingen. Ook bij patiënten met een matig of hoog risico wordt actief volgen verwogen indien er naast de leeftijd sprake is van duidelijke co0morbiditeit die de levensverwachting negatief beïnvloedt. | Intermediate (2+3) |
| | | | |
| **NICE 2008** | Until June 2007 | Men with low-risk localised prostate cancer who are considered suitable for radical treatment should first be offered active surveillance. | Low |
| | | Active surveillance is particularly suitable for a subgroup of men with low-risk localised prostate cancer who have clinical stage T1c, a Gleason score 3+3, a PSA density < 0.15 ng/ml/ml and who have cancer in less than 50% of their total number of biopsy cores with < 10mm of any core involved. | Low |
| | | Active surveillance should be discussed as an option with men who have intermediate-risk localised prostate cancer. | Low |
| | | Active surveillance is not recommended for men with high-risk localised prostate cancer. | Low |
| **EAU 2011 Indications** | Until Jan 2010 | Inclusion criteria for active surveillance with the lowest risk of cancer progression are: PSA < 10 ng/ml, biopsy Gleason score < 6, < 2 positive biopsies, < 50% cancer per biopsy, cT1c-2a. | Low |
| | | Stage T1a: well and moderately differentiated tumours. In younger patients with a life expectancy of > 10 years, re-evaluation with PSA, TRUS and biopsies of the prostatic remnant is recommended | Moderate (2A) |
| | | Stage T1b-T2b: well and moderately differentiated tumours. In asymptomatic patients with a life expectancy of < 10 years | Moderate (2A) |

| | | | | |
|---|---|---|---|---|
| **EAU 2011 Options** | Until 2010 | Jan | In presumed localised PCa (Nx-N0, M0):<br>Stage T1b-T2b patients who are well informed and have well-differentiated (or Gleason 2-4) PCa and a life expectancy of 10-15 years.<br>All patients not willing to accept side-effects of active treatment.<br>Well-informed, asymptomatic patients with high PSA levels for whom cure is unlikely | Low |
| **Aragon 2008** | Until 2007 | Nov | In patients with clinically localised prostate cancer with a life expectancy exceeding 10 years, radical prostatectomy or external beam radiotherapy is recommended | Moderate (B) |
| | | | In patients with clinically localised prostate cancer with a life expectancy below 10 years, watchful waiting may be an alternative. | Moderate (B) |
| | | | In patients with clinically localised prostate cancer at low risk, Gleason < 3 + 3, < 50% affected cylinders in the biopsy and PSA < 15 ng/ml, active surveillance can be offered as an alternative to immediate radical treatment. | Very Low (C) |

# APPENDIX 6. GRADE

## Appendix 6.1. Levels of evidence

| Quality level | Definition | Methodological Quality of Supporting Evidence |
|---|---|---|
| **High (A)** | 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 (B)** | 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 (C)** | 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 (C)** | **We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect** | |

## Appendix 6.2. Down- or upgrading the evidence

| Study Design | Quality of Evidence | Lower if | Higher if |
|---|---|---|---|
| Randomized trial → | High | Risk of bias<br>-1 Serious<br>-2 Very serious | Large effect<br>+1 Large<br>+2 Very large |
| | Moderate | Inconsistency<br>-1 Serious<br>-2 Very serious | Dose response<br>+1 Evidence of a gradient |
| Observational study → | Low | Indirectness<br>-1 Serious<br>-2 Very serious | All plausible confounding<br>+1 Would reduce a demonstrated effect or |
| | Very low | Imprecision<br>-1 Serious<br>-2 Very serious | +1 Would suggest a spurious effect when results show no effect |
| | | Publication bias<br>-1 Likely<br>-2 Very likely | |

## Appendix 6.3. Strength of recommendations

### *Appendix 6.3.1. Definitions*

| Grade | Definition |
|---|---|
| **Strong** | **The desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not** |
| **Weak** | **The desirable effects of an intervention probably outweigh the undesirable effects, or probably do not** |

### *Appendix 6.4.1. Factors that influence 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—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted** |

## Appendix 6.5. Grade Profile

### *Appendix 6.5.1. 3.8.4. Men with life expectancy < 10 years*

- **In patients with localised prostate cancer and life expectancy < 10 years or with important comorbidities watchful waiting with palliative intent is recommended.**

| Results | No. of studies | 1 | 2 | 3 | 4 | 5 | Reasons for downgrading | GRADE |
|---|---|---|---|---|---|---|---|---|
| After a median follow-up of 10 years, RP did not significantly reduce all-cause mortality: HR=0.88 (0.71 to 1.08); P = 0.22[24] | 1 (PIVOT) | | | | 1 | | Imprecision : Insufficient sample size | Moderate |

*1 : limitations of design, 2 :inconsistency, 3 : indirectness, 4 : imprecision, 5 :publication bias*

- **Strong recommendation based on side effects of radical treatment (see point 3.4.2.for morbidity and point 3.4.3 for quality of life).**

### *Appendix 6.5.2. Low-risk localised prostate cancer*

- **In patients with low-risk localised prostate cancer, eligible and opting for a strategy with curative intent, active surveillance can be considered as a management option, taking into account patient preferences and health conditions related to urinary, sexual, and bowel function.**

| Results | No. of studies | 1 | 2 | 3 | 4 | 5 | Reasons for downgrading | GRADE |
|---|---|---|---|---|---|---|---|---|
| After a median follow-up of 10 years, a mong men with low-risk tumours (n=296), radical prostatectomy increased not significantly all-cause mortality: HR=1.15 (0.80 to 1.66) | 1 (PIVOT) | | | 1 | 1 | | Indirectness: follow-up in PIVOT trial is described as watchful waiting, not as active surveillance<br>Imprecision : Insufficient sample size (wide CI) | Low |

*1 : limitations of design, 2 :inconsistency, 3 : indirectness, 4 : imprecision, 5 :publication bias*

- **Strong recommendation based on side effects of radical treatment (see point 3.4.2. for morbidity and point 3.4.3 for quality of life).**

## *Appendix 6.5.3. Intermediate-risk localised prostate cancer*

- **In patients with intermediate-risk localised prostate cancer and particularly those with important co-morbidities and life expectancy < 10years, eligible and opting for a strategy with curative intent, active surveillance should be discussed as a management option taking into account patient preferences and health conditions related to urinary, sexual, and bowel function.**

| Results | No. of studies | 1 | 2 | 3 | 4 | 5 | Reasons for downgrading | GRADE |
|---|---|---|---|---|---|---|---|---|
| After a median follow-up of 10 years, among men with intermediate-risk tumours (n=249), radical prostatectomy reduced significantly all-cause mortality: HR=0.69 (0.49 to 0.98) | 1 (PIVOT) | | | 1 | 1 | | Indirectness: follow-up in PIVOT trial is described as watchful waiting, not as active surveillance<br>Imprecision : Insufficient sample size | Low |

*1 : limitations of design, 2 :inconsistency, 3 : indirectness, 4 : imprecision, 5 :publication bias*

- **Strong recommendation based on side effects of radical treatment, especially for men with life-expectancy < 10 y (see point 3.4.2. for morbidity and point 3.4.3 for quality of life).**

## *Appendix 6.5.4. High-risk localised prostate cancer*

- **In patients with high-risk localised prostate cancer, active surveillance is not recommended.**

| Results | No. of studies | 1 | 2 | 3 | 4 | 5 | Reasons for downgrading | GRADE |
|---|---|---|---|---|---|---|---|---|
| After a median follow-up of 10 years, among men with high-risk tumours (n=157), radical prostatectomy reduced not significantly all-cause mortality: HR=0.69 (0.16 to 1.00) | 1 (PIVOT) | | | 1 | 1 | | Indirectness: follow-up in PIVOT trial is described as watchful waiting, not as active surveillance<br>Imprecision : Insufficient sample size | Low |

*1 : limitations of design, 2 :inconsistency, 3 : indirectness, 4 : imprecision, 5 :publication bias*

- **Weak recommendation because CI is near 1. Recommendation may change in further study with larger sample size.**

**Confirmatory biopsy**

- **A biopsy is recommended one year after the diagnosis.**

Level of evidence is low because based on results of the three observational studies.[38, 41, 43] They found that the most cases of disease reclassification seem to follow the confirmatory biopsy.

- **Strong recommendation, low level of evidence.**

**Other tests**

- **PSA measurements every six months, clinical examination or MRI every year each, can be considered.**

Level of evidence is low because based on conclusions of the two observational studies.[41, 43] Level of recommendation is weak. Due to the lack of study focused on active surveillance, we found no effect of tests on outcomes.

- **Weak recommendation, low level of evidence.**

**Routine biopsy**

- **After the biopsy performed at one year, routine biopsy at years 4, 7 and 10 should be considered.**
- **GCP based on guidelines.**

**Life expectancy < 10y**

- **After the age of 80 or in case of life expectancy < 10 year, or in case of significant comorbidity development, it's recommended to stop performing routine biopsy and to offer watchful waiting with palliative intent.**

As for 3.8.4

- **Strong recommendation, moderate level of evidence.**

**Disease reclassification**

- **PSA>10ng/mL, or PSADT< 3years or clinical change or suspicious lesions at mpMRI should be confirmed by additional biopsy.Disease reclassification is achieved after demonstration of an increase in stage or in Grade (Gleason score ≥ 7).**

Level of evidence is low because based on results of the three observational studies.[38, 41, 43]

- **Strong recommendation, low level of evidence.**
- **Switching to a radical treatment should be reconsidered in case of disease reclassification.**

This recommendation refers to 3.8.5., 3.8.6, 3.8.7.

GCP based on guidelines

# APPENDIX 7. LIFE EXPECTANCY TABLE IN BELGIUM

| 2007-2009 | BELGIQUE | | | | | |
|---|---|---|---|---|---|---|
| | Hommes | | | | | |
| **Age révolu (x)** | Population observée (px) | Décès observés (dx) | Probabilité de décès (Qx) | Survivants (Lx) | Décès de la table (Dx) | Espérance de vie (Ex) |
| **birth** | 194.915 | 696 | 0,003571 | ######## | 3.571 | 76,89 |
| **0** | 188.936 | 162 | 0,000857 | 996.429 | 854 | 76,66 |
| **1** | 187.982 | 58 | 0,000309 | 995.575 | 307 | 75,73 |
| **2** | 186.065 | 32 | 0,000172 | 995.268 | 171 | 74,75 |
| **3** | 182.533 | 41 | 0,000225 | 995.096 | 224 | 73,76 |
| **4** | 179.585 | 22 | 0,000123 | 994.873 | 122 | 72,78 |
| **5** | 178.603 | 17 | 0,000095 | 994.751 | 95 | 71,79 |
| **6** | 180.234 | 19 | 0,000105 | 994.656 | 105 | 70,80 |
| **7** | 181.236 | 13 | 0,000072 | 994.552 | 71 | 69,80 |
| **8** | 182.278 | 17 | 0,000093 | 994.480 | 93 | 68,81 |
| **9** | 182.887 | 11 | 0,000060 | 994.387 | 60 | 67,82 |
| **10** | 184.413 | 22 | 0,000119 | 994.328 | 119 | 66,82 |
| **11** | 185.094 | 22 | 0,000119 | 994.209 | 118 | 65,83 |
| **12** | 185.572 | 31 | 0,000167 | 994.091 | 166 | 64,83 |
| **13** | 187.990 | 28 | 0,000149 | 993.925 | 148 | 63,85 |
| **14** | 193.114 | 40 | 0,000207 | 993.777 | 206 | 62,86 |
| **15** | 198.382 | 62 | 0,000313 | 993.571 | 311 | 61,87 |
| **16** | 201.313 | 63 | 0,000313 | 993.260 | 311 | 60,89 |
| **17** | 200.595 | 120 | 0,000598 | 992.950 | 594 | 59,91 |
| **18** | 198.569 | 131 | 0,000660 | 992.356 | 655 | 58,94 |
| **19** | 195.885 | 150 | 0,000766 | 991.701 | 759 | 57,98 |
| **20** | 194.812 | 166 | 0,000852 | 990.941 | 844 | 57,02 |
| **21** | 192.166 | 179 | 0,000931 | 990.097 | 922 | 56,07 |
| **22** | 191.744 | 160 | 0,000834 | 989.175 | 825 | 55,12 |
| **23** | 192.446 | 173 | 0,000899 | 988.349 | 888 | 54,17 |
| **24** | 196.582 | 145 | 0,000738 | 987.461 | 728 | 53,22 |
| **25** | 201.539 | 163 | 0,000809 | 986.733 | 798 | 52,26 |
| **26** | 205.604 | 185 | 0,000900 | 985.935 | 887 | 51,30 |
| **27** | 207.971 | 175 | 0,000841 | 985.047 | 829 | 50,34 |
| **28** | 208.002 | 200 | 0,000962 | 984.219 | 946 | 49,39 |
| **29** | 207.010 | 186 | 0,000899 | 983.272 | 883 | 48,43 |
| **30** | 205.482 | 183 | 0,000891 | 982.389 | 875 | 47,48 |
| **31** | 203.957 | 200 | 0,000981 | 981.514 | 962 | 46,52 |
| **32** | 205.488 | 190 | 0,000925 | 980.551 | 907 | 45,56 |
| **33** | 209.828 | 228 | 0,001087 | 979.645 | 1.064 | 44,61 |
| **34** | 217.477 | 246 | 0,001131 | 978.580 | 1.107 | 43,65 |
| **35** | 224.352 | 254 | 0,001132 | 977.473 | 1.107 | 42,70 |
| **36** | 230.089 | 248 | 0,001078 | 976.367 | 1.052 | 41,75 |
| **37** | 232.700 | 319 | 0,001371 | 975.314 | 1.337 | 40,79 |
| **38** | 233.329 | 330 | 0,001414 | 973.977 | 1.378 | 39,85 |
| **39** | 234.076 | 382 | 0,001632 | 972.600 | 1.587 | 38,91 |
| **40** | 237.124 | 387 | 0,001632 | 971.012 | 1.585 | 37,97 |
| **41** | 242.726 | 428 | 0,001763 | 969.428 | 1.709 | 37,03 |
| **42** | 249.105 | 484 | 0,001943 | 967.718 | 1.880 | 36,09 |
| **43** | 252.109 | 542 | 0,002150 | 965.838 | 2.076 | 35,16 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **44** | 251.012 | 644 | 0,002566 | 963.762 | 2.473 | 34,24 |
| **45** | 247.325 | 622 | 0,002515 | 961.289 | 2.418 | 33,33 |
| **46** | 244.272 | 698 | 0,002857 | 958.872 | 2.740 | 32,41 |
| **47** | 243.014 | 777 | 0,003197 | 956.132 | 3.057 | 31,50 |
| **48** | 240.565 | 877 | 0,003646 | 953.074 | 3.475 | 30,60 |
| **49** | 237.006 | 985 | 0,004156 | 949.600 | 3.947 | 29,71 |
| **50** | 231.702 | 1.086 | 0,004687 | 945.653 | 4.432 | 28,83 |
| **51** | 226.716 | 1.213 | 0,005350 | 941.221 | 5.036 | 27,96 |
| **52** | 222.007 | 1.260 | 0,005675 | 936.185 | 5.313 | 27,11 |
| **53** | 217.690 | 1.307 | 0,006004 | 930.872 | 5.589 | 26,26 |
| **54** | 214.051 | 1.402 | 0,006550 | 925.283 | 6.060 | 25,42 |
| **55** | 208.464 | 1.502 | 0,007205 | 919.223 | 6.623 | 24,58 |
| **56** | 204.465 | 1.630 | 0,007972 | 912.600 | 7.275 | 23,76 |
| **57** | 200.828 | 1.758 | 0,008754 | 905.324 | 7.925 | 22,95 |
| **58** | 200.446 | 1.835 | 0,009155 | 897.399 | 8.215 | 22,14 |
| **59** | 199.070 | 2.014 | 0,010117 | 889.184 | 8.996 | 21,34 |
| **60** | 197.564 | 2.185 | 0,011060 | 880.188 | 9.735 | 20,56 |
| **61** | 184.988 | 2.251 | 0,012168 | 870.453 | 10.592 | 19,78 |
| **62** | 173.174 | 2.217 | 0,012802 | 859.861 | 11.008 | 19,02 |
| **63** | 158.468 | 2.194 | 0,013845 | 848.853 | 11.752 | 18,26 |
| **64** | 148.160 | 2.308 | 0,015578 | 837.101 | 13.040 | 17,51 |
| **65** | 133.864 | 2.207 | 0,016487 | 824.061 | 13.586 | 16,78 |
| **66** | 126.861 | 2.236 | 0,017626 | 810.475 | 14.285 | 16,05 |
| **67** | 128.951 | 2.419 | 0,018759 | 796.189 | 14.936 | 15,33 |
| **68** | 135.635 | 2.810 | 0,020717 | 781.254 | 16.186 | 14,61 |
| **69** | 136.289 | 3.071 | 0,022533 | 765.068 | 17.239 | 13,91 |
| **70** | 131.924 | 3.186 | 0,024150 | 747.829 | 18.060 | 13,22 |
| **71** | 126.058 | 3.356 | 0,026623 | 729.769 | 19.428 | 12,54 |
| **72** | 121.978 | 3.543 | 0,029046 | 710.340 | 20.633 | 11,86 |
| **73** | 119.103 | 4.027 | 0,033811 | 689.708 | 23.320 | 11,20 |
| **74** | 117.164 | 4.333 | 0,036982 | 666.388 | 24.645 | 10,58 |
| **75** | 114.160 | 4.654 | 0,040767 | 641.743 | 26.162 | 9,97 |
| **76** | 110.377 | 5.144 | 0,046604 | 615.581 | 28.688 | 9,37 |
| **77** | 102.704 | 5.318 | 0,051780 | 586.893 | 30.389 | 8,80 |
| **78** | 94.011 | 5.375 | 0,057174 | 556.503 | 31.818 | 8,26 |
| **79** | 85.112 | 5.487 | 0,064468 | 524.686 | 33.825 | 7,73 |
| **80** | 77.839 | 5.438 | 0,069862 | 490.860 | 34.293 | 7,22 |
| **81** | 71.493 | 5.645 | 0,078959 | 456.568 | 36.050 | 6,73 |
| **82** | 64.973 | 5.771 | 0,088822 | 420.518 | 37.351 | 6,26 |
| **83** | 58.125 | 5.847 | 0,100594 | 383.167 | 38.544 | 5,82 |
| **84** | 50.637 | 5.635 | 0,111282 | 344.623 | 38.350 | 5,42 |
| **85** | 43.632 | 5.409 | 0,123969 | 306.272 | 37.968 | 5,04 |
| **86** | 36.941 | 5.171 | 0,139980 | 268.304 | 37.557 | 4,68 |
| **87** | 28.413 | 4.231 | 0,148911 | 230.747 | 34.361 | 4,36 |
| **88** | 19.245 | 3.240 | 0,168355 | 196.386 | 33.063 | 4,03 |
| **89** | 12.204 | 2.231 | 0,182809 | 163.324 | 29.857 | 3,75 |
| **90** | 8.614 | 1.680 | 0,195031 | 133.467 | 26.030 | 3,47 |
| **91** | 7.479 | 1.696 | 0,226768 | 107.436 | 24.363 | 3,19 |
| **92** | 6.560 | 1.574 | 0,239939 | 83.073 | 19.933 | 2,98 |
| **93** | 5.301 | 1.412 | 0,266365 | 63.141 | 16.818 | 2,77 |
| **94** | 3.877 | 1.100 | 0,283725 | 46.322 | 13.143 | 2,59 |
| **95** | 2.589 | 788 | 0,304365 | 33.179 | 10.099 | 2,42 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **96** | 1.690 | 605 | 0,357988 | 23.081 | 8.263 | 2,26 |
| **97** | 1.048 | 330 | 0,314885 | 14.818 | 4.666 | 2,24 |
| **98** | 669 | 223 | 0,333333 | 10.152 | 3.384 | 2,04 |
| **99** | 411 | 167 | 0,406326 | 6.768 | 2.750 | 1,80 |
| **100** | 218 | 90 | 0,412844 | 4.018 | 1.659 | 1,69 |
| **101** | 120 | 52 | 0,433333 | 2.359 | 1.022 | 1,53 |
| **102** | 70 | 29 | 0,414286 | 1.337 | 554 | 1,33 |
| **103** | 39 | 23 | 0,589744 | 783 | 462 | 0,91 |
| **104+** | 19 | 9 | 1,000000 | 321 | 321 | 0,17 |

*Cette table de mortalité a été revue et corrigée pour mieux correspondre au type de quotients utilisés (une note explicative complète sur ce sujet est en préparation). Les changements principaux concernent :*
*- la série des âges (qui commence par «birth», représentant l'âge exact 0, se poursuit par les âges révolus et se clôture par l'âge «104+») et*
*- le calcul de l'espérance de vie (moyenne arithmétique des âges au décès de la table à partir d'un âge donné, diminuée du nombre d'années déjà vécues pour atteindre cet âge).*

*SOURCE : SPF Économie - Direction générale Statistique et Information économique.*
*http://statbel.fgov.be*

# APPENDIX 8. QUALITY CRITERIA FOR PROSTATE BIOPSY

We put here some important discussions around quality criteria for prostate biopsy.

**HGPIN**

*Question* : it remains unclear if and how many nucleoli are needed to diagnose HGPIN (Egevad et al. Mod Pathol 19:180).

*Answer* : In my opinion, this point is out of the subject of "Active surveillance in prostate adenocarcinoma".

The diagnostic criteria for prostatic intraepithelial neoplasia (LGPIN and HGPIN) are quite well described by D. Bostwick in the Urologic Surgical Pathology 2nd Edition.

Because of its lack of specificity, it is recommended that LGPIN should not be reported (Strigley JR et al., Arch Pathol Lab Med 2000). As noted by J. Epstein and M. Herawi in Journal of Urology 2006 and by others, only multifocal HGPIN seems to be associated with an increase risk of cancer on repeat biopsy.

Comment : The categories of diseases 3 & 4. High grade prostatic intraepithelial neoplasia (HGPIN) and atypical glands suspicious for cancer (ASAP) should never be diagnosed as cancer and never treated as cancer by the clinician.

**Extent of tumour involvement of cores**

*Question:* if tumour is discontinuously present in a core, do we suggest to collaps the tumour by disregarding intervening stroma or not? (see for example Karram et al. Am J Surg Pathol 35:1351).

*Answer:* Currently, there is no evidence one method is better than the other, but it might be relevant to put forward one method, so the same method will be used throughout Belgium (in my opinion, most non-uropathologists are even not aware of the existence of two systems).

I agree with the remark. As said by Fine et al European Urology 2012, evidences are too limited to draw a definitive conclusion about the method to use. However, the study recently published by Karram S et al. (Am J Surg Pathol 2011) demonstrated that for prostate cancer in which the

needle biopsy grade is representative of the entire tumour, quantifying cancer extent on biopsy by measuring discontinuous cancer on biopsy from one end to the other as opposed to "collapsing" the cancer by subtracting out the intervening benign prostate tissue correlates better with organ-confined disease and risk of positive margins. For this reason, I added the reference in the text.

**Perineural and lymphovascular invasion**

*Question*: there is no international consensus regarding the reporting of these features in needle biopsies; especially for perineural invasion there is no agreement. The ISUP consensus on prostatectomies suggested that lymphovascular invasion should be reported, but there is no guideline for perineural invasion on prostatectomies (see series of articles in January 2010 issue of Mod Pathol). Findings on prostatectomy studies cannot be extrapolated to needle biopsies (see Freeman. Surg Oncol 18:200) and several studies show that the clinical relevance of reporting perineural invasion on needle biopsies is still to be proven (Al-Hussain et al. J Urol 186:470, Harnden et al. Cancer 109:13).

*Answer:* I agree with the remark. The sentence: “Perineural and lymphovascular invasion are currently not considered as essential reporting elements for prostatic needle biopsies by leading international urological pathologists” is added in the text.

**Gleason grading**

*Comments :* this is of course pivotal and nicely addressed by the already included reference (ISUP 2005 modified Gleason).Special attention has to be given regarding the accuracy of reporting Gleason patterns. While undergrading has been an issue, it appears that currently there is a tendency to overgrade (see for example Egevad et al. Histopathology, accepted article). There exist several tools to train Gleason grading, e.g. Web-tutorials (http://162.129.103.34/prostate/index.htm#consensus).The webside might be included in specific recommendation for pathologists or in reference.The current text refers to primary and secondary patterns; it might be considered to add a statement that the 2005 ISUP guidelines should also be followed in case of minor secondary patterns and tertiary patterns (especially since the latter is differently reported on needle and prostatectomy specimens). Furthermore, the 2005 guidelines could not reach a conclusion regarding grading of glomeruloid structures; more recent data suggest that they should be graded as Gleason 4 (Lotan et al. Hum Pathol 40:471).Recommendations published by Fine SW et al. (2012) for special Gleason grading scenarios such as the context of abundant high-grade cancer, prostate cancer variants, glomeruloid structures and/or the presence of a tertiary Gleason pattern in prostate biopsies (Fine SW et al. European Urology 2012) is now added in the text.

# APPENDIX 9. EXPERTS AND STAKEHOLDERS FINAL REVIEW

Letter to stakeholders in preparation of stakeholders meeting:

**Instructions for scoring the recommendations**

Please score each recommendation on a 5-point scale to indicate your agreement with the recommendation: a score of ‘1’ indicates ‘completely disagree’, ‘2’ indicates ‘somewhat disagree’, ‘3’ indicates ‘unsure’, ‘4’ indicates ‘somewhat agree’, and ‘5’ indicates ‘completely agree’. You can also answer ‘not applicable’ (NA) in case you are not familiar with the underlying evidence.

In case you disagree with the recommendation (score ‘1’ or ‘2’), please provide the scientific evidence (which of course should at least be better than the presented evidence).

The scores should be sent back by Tuesday November, 20th at the latest to francoise.mambourg@kce.fgov.be. Scores received afterwards will not be taken into account. The scores will then be anonymised and summarised into a median score, range and % of ‘agree’-scores . The scores will be presented at the open meeting on Tuesday November 27th, 18.00-20.00h at the KCE, and serve to focus the discussion.

| Item | Recommendations before stakeholders meeting | Recommendations after stakeholders meeting | GOR | LoE | 5 | 4 | % 4 or 5 |
|---|---|---|---|---|---|---|---|
| **Chapter 3. WATCHFUL WAITING / ACTIVE SURVEILLANCE** | | | | | | | |
| 3.8.1 | A guideline with criteria of a good quality biopsy (as well for TRUS-guided as for MRI-guided biopsy) is needed not only for the pathologists but also for the urologists | A guideline with quality criteria of a prostate biopsy is needed not only for pathologists but also for urologists and radiologists | GCP | | 10 | 2 | 100% |
| 3.8.2 | An assessment should be undertaken before any treatment decisions can be made. This assessment should include: (1) the patient's overall health status, his life expectancy and comorbidities and (2) the quality of the biopsy and tumour characteristics (including the risk category) | An assessment should be undertaken before any treatment decisions can be made. This assessment should include: (1) the patient's overall health status, his life expectancy and comorbidities and (2) the quality of the biopsy and tumour characteristics (including the risk category) | GCP | | 7 | 4 | 92% |
| 3.8.3 | A patient with clinically localised prostate cancer, eligible and opting for a strategy with curative intent, should be informed about commonly accepted initial managements with regards to his health status, 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. | A patient with clinically localised prostate cancer, eligible and opting for a strategy with curative intent, should be informed about commonly accepted initial managements with regards to his health status, 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. | GCP | | 11 | 0 | 100% |
| 3.8.4 | In patients with localised prostate cancer and life expectancy < 10 years or with important comorbidities watchful waiting with palliative intent is recommended. | In patients with localised prostate cancer and life expectancy < 10 years or with important comorbidities, watchful waiting with palliative intent is recommended. | Strong | Moderate | 2 | 4 | 60% |
| 3.8.5 - 1 | In patients with low-risk localised prostate cancer, eligible and opting for a strategy with curative intent, active surveillance can be considered as a management option, taking into account patient preferences and health conditions related to urinary, sexual, and bowel function. | 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. | Strong | Low | 8 | 2 | 100% |
| 3.8.5 - 2 | Men with low-risk localised prostate cancer must be informed that at the present time there is no demonstrated benefit to be immediately treated. | Men with low-risk localised prostate cancer must be informed that at the present time there is no demonstrated benefit for immediate treatment. | GCP | | 5 | 1 | 60% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 3.8.6 | In patients with intermediate-risk localised prostate cancer and particularly those with important co-morbidities and life expectancy <10years, eligible and opting for a strategy with curative intent, active surveillance should be discussed as a management option taking into account patient preferences and health conditions related to urinary, sexual, and bowel function. | Because of the heterogeneity of the patients with intermediate-risk localised prostate cancer, no general recommendation can currently be made on active surveillance in this subset of patients. | Strong | Low | 4 | 3 | 70% |
| 3.8.7 | In patients with high-risk localised prostate cancer, active surveillance is not recommended. | In patients with high-risk localised prostate cancer, active surveillance is not recommended. | Weak | Low | 8 | 2 | 100% |
| | | | | | | | |
| 4.6.1 | A repeat biopsy is recommended one year after the diagnosis. | A repeat biopsy is recommended one year after the diagnosis. | Strong | Low | 7 | 4 | 100% |
| 4.6.2 | PSA measurements every six months and clinical examination or MRI every year each, can be considered. | PSA measurements and clinical examination every six months can be considered. Imaging each year can be considered. | Weak | Low | 5 | 6 | 92% |
| 4.6.3 | After the biopsy performed at one year, routine biopsy at years 4, 7 and 10 should be considered | After the biopsy performed at one year, routine biopsy at years 4, 7 and 10 can be considered | GCP | | 1 | 6 | 70% |
| 4.6.4 | After the age of 80, or in case of life expectancy <10 year, or in case of the development of significant comorbidity it is recommended to stop performing routine biopsies and to offer watchful waiting with palliative intent. | After the age of 80, or in case of life expectancy <10 year, or in case of the development of significant comorbidity it is recommended to stop performing routine biopsies and to offer watchful waiting with palliative intent. | Strong | Moderate | 7 | 4 | 92% |
| 4.6.5 -1 | Disease progress as suggested by PSA>10ng/mL, or PSADT< 3 years , or clinical change, or suspicious lesions at mpMRI, should be confirmed by an additional biopsy. Disease reclassification is achieved after demonstration of an increase in stage or in Grade (Gleason score ≥7). | Disease progression as suggested by PSA>10ng/mL, or PSADT< 3 years, or clinical change, or suspicious lesions at imaging, should be confirmed by an additional biopsy and followed by risk reclassification. | Strong | Low | 6 | 4 | 90% |
| 4.6.5 - 2 | Switching to a radical treatment should be considered in case of disease reclassification. | Switching to a radical treatment should be considered in case of risk reclassification. | GCP | | 7 | 4 | 100% |

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