

# Diagnosis, staging and treatment of patients with prostate cancer

National Clinical Guideline No. 8

**Summary**

### Guideline Development Group

The National Clinical Guideline on the diagnosis, staging and treatment of patients with prostate cancer in Ireland was developed by the National Cancer Control Programme (NCCP), in collaboration with clinicians, librarians and stakeholder groups.



### Referencing this National Clinical Guideline Summary

National Clinical Guideline No. 8 should be referenced as follows:

Department of Health. Diagnosis, staging and treatment of patients with prostate cancer. National Clinical Guideline No. 8 Summary. June 2015. ISSN 2009-6267.

This Guideline Summary should be read in conjunction with the full version National Clinical Guideline.

The full version of this National Clinical Guideline, is available on the website:  
[www.health.gov.ie/patient-safety/ncec](http://www.health.gov.ie/patient-safety/ncec)

The complete list of references can be found in the full version of the National Clinical Guideline.

### Notice to Health Professionals and Disclaimer

The Guideline Development Group's expectation is that health professionals will use clinical knowledge and judgment in applying the principles and recommendations contained in this guideline. These recommendations may not be appropriate in all circumstances and it may be necessary to deviate from this guideline. Clinical judgment in such a decision must be clearly documented. Care options should be discussed with the patient, his/her significant other(s), and the multidisciplinary team on a case-by-case basis as necessary.

## National Clinical Effectiveness Committee

The National Clinical Effectiveness Committee (NCEC) was established as part of the Patient Safety First Initiative. The NCEC is a partnership between key stakeholders in patient safety. NCEC's mission is to provide a framework for national endorsement of clinical guidelines and audit to optimise patient and service user care. The NCEC has a remit to establish and implement processes for the prioritisation and quality assurance of clinical guidelines and clinical audit so as to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit.

The aim of the suite of National Clinical Guidelines is to provide guidance and standards for improving the quality, safety and cost-effectiveness of healthcare in Ireland. The implementation of these National Clinical Guidelines will support the provision of evidence-based and consistent care across Irish healthcare services.

### NCEC Terms of Reference

1. Provide strategic leadership for the national clinical effectiveness agenda.
2. Contribute to national patient safety and quality improvement agendas.
3. Publish standards for clinical practice guidance.
4. Publish guidance for National Clinical Guidelines and National Clinical Audit.
5. Prioritise and quality assure National Clinical Guidelines and National Clinical Audit.
6. Commission National Clinical Guidelines and National Clinical Audit.
7. Align National Clinical Guidelines and National Clinical Audit with implementation levers.
8. Report periodically on the implementation and impact of National Clinical Guidelines and the performance of National Clinical Audit.
9. Establish sub-committees for NCEC workstreams.
10. Publish an Annual Report.

The full version of this guideline and further information on the NCEC and endorsed National Clinical Guidelines is available at: <http://health.gov.ie/patient-safety/ncec/>

## Using this National Cancer Control Programme National Clinical Guideline

The NCCP is part of the Health Service Executive (HSE) and was established in 2007 to implement the recommendations of the National Cancer Strategy. The NCCP is responsible for national cancer control by helping to prevent cancer, treat cancer and increase survival and quality of life for those who develop cancer, by converting the knowledge gained through research and surveillance into strategies and actions. The need to follow evidence-based clinical guidelines covering a patient's journey from early detection, diagnosis, treatment, monitoring and end-of-life care is a key priority for the NCCP.

It is critical to have a range of health professionals working together to plan and deliver care for cancer patients. The target users of the guideline are the multidisciplinary clinical team caring for patients with prostate cancer.

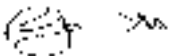
The development of this National Clinical Guideline would not have been possible without the enormous contribution of the members of the Guideline Development Group (GDG), the NCCP Guideline Steering Group and the reviewers. We are grateful for the commitment shown by all who contributed to the development of this guideline. In particular the invaluable input of the clinicians and the HSE/hospital librarians in this process is acknowledged and we thank them for giving generously of their time and expertise.

This full version of this National Clinical Guideline is available at:  
[www.health.gov.ie/patient.safety/ncec](http://www.health.gov.ie/patient.safety/ncec) and [www.hse.ie/cancer](http://www.hse.ie/cancer)

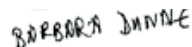
This Guideline Summary should be read in conjunction with the National Clinical Guideline Full Version.



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# 1 Definition and impact of prostate cancer

## 1.1 Need for National Clinical Guideline

In 2006, the second national cancer strategy, A Strategy for Cancer Control in Ireland (DoHC, 2006), advocated a comprehensive cancer control programme. It was recommended that national site-specific multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care. The principal objective of developing these guidelines is to improve the quality of care received by patients. Other objectives include:

- Improvements in the quality of clinical decisions,
- Improvement in patient outcomes,
- Potential for reduction in morbidity and mortality and improvement in quality of life,
- Promotion of interventions of proven benefit and discouragement of ineffective ones, and
- Improvements in the consistency and standard of care.

## 1.2 Clinical impact of prostate cancer

The diagnosis, staging and treatment of patients with prostate cancer requires multidisciplinary care in an acute hospital setting. The majority of patients will require diagnostic tests (radiology, pathology) and depending on the treatment plan may require surgery, chemotherapy and radiation therapy. A proportion of patients may also require palliative care.

## 1.3 Scope of National Clinical Guideline

This National Clinical Guideline was developed to improve the standard and consistency of clinical practice in line with the best and most recent scientific evidence available.

The guideline focuses on the diagnosis, staging and treatment of patients with prostate cancer. This guideline does not include recommendations covering every aspect of diagnosis, staging and treatment. This guideline focuses on areas of clinical practice:

- known to be controversial or uncertain,
- where there is identifiable variation in practice,
- where there is new or emerging evidence,
- where guidelines have potential to have the most impact.

For information on NCCP general practitioner (GP) referral guidelines, standardised GP referral forms, and GP electronic referral for patients with prostate cancer and the cancer survivorship programme, see the full version of this National Clinical Guideline.

Patient information booklets/leaflets covering various aspects of the cancer journey are available on the NCCP website.

The NCCP have prioritised the development of clinical guidelines for those cancers that have the highest burden of illness. Prostate Cancer is now the largest solid tumour diagnosed annually in Ireland.

Patients that are covered by this guideline are:

- Adults (18 years or older) with newly diagnosed prostate cancer
- Adults with metastases arising from prostate cancer.

## 1.4 Levels of evidence and grading of recommendations

Tables 1 to 4 outline the categories used for levels of evidence and grading of recommendations.

**Table 1** Levels of evidence for diagnostic studies (Oxford CEBM, 2009)

<b>1a</b>	Systematic review (with homogeneity*) of Level 1 diagnostic studies; clinical decision rule (CDR") with 1b studies from different clinical centres.
<b>1b</b>	Validating** cohort study with good reference standards" " "; or CDR tested within one clinical centre.
<b>1c</b>	Absolute SpPins (specificity) and SnNouts (sensitivity)" " ".
<b>2a</b>	Systematic review (with homogeneity*) of Level >2 diagnostic studies.
<b>2b</b>	Exploratory** cohort study with good reference standards; CDR after deviation, or validated only on split-samples§§§ or databases.
<b>3a</b>	Systematic review (with homogeneity*) of 3b and better studies.
<b>3b</b>	Non-consecutive study; or without consistently applied reference standards.
<b>4</b>	Case-control study, poor or non-independent reference standard.
<b>5</b>	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

\* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

" Clinical Decision Rule (these are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category).

\*\* Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.

" " " Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

" " An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a negative result rules-out the diagnosis.

§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

**Table 2** Grades of recommendations for diagnostic studies (Oxford CEBM, 2009)

<b>A</b>	Consistent level 1 studies.
<b>B</b>	Consistent level 2 or 3 studies; or Extrapolations from level 1 studies.
<b>C</b>	Level 4 studies; or Extrapolations from level 2 or 3 studies.
<b>D</b>	Level 5 evidence; or Troublingly inconsistent or inconclusive studies of any level.

*Extrapolations are where data is used in a situation that has potentially clinically important differences than the original study situation.*



**Table 3** Levels of evidence for interventional studies (SIGN grading system 1999-2012)

<b>1++</b>	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
<b>1+</b>	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
<b>1-</b>	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
<b>2++</b>	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
<b>2+</b>	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
<b>2-</b>	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
<b>3</b>	Non-analytic studies (e.g. case reports, case series).
<b>4</b>	Expert opinion.

**Table 4** Grades of recommendations for interventional studies (SIGN grading system 1999-2012)

<b>A</b>	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
<b>B</b>	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
<b>C</b>	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
<b>D</b>	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

*Note: the grade of recommendation does not necessarily reflect the clinical importance of the recommendation.*

**Good practice point**

Recommended best practice based on the clinical experience of the GDG.



## 2 National Clinical Guideline recommendations

### 2.1 Summary of clinical recommendations

Responsibility for implementation: While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline. Each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

There are various entry points for patients within the scope of this guideline.

#### Defining risk categories

- 2.2.1.1** It is recommended that the risk categories stated are used when interpreting and placing patients into risk groups.
- **Low-risk:** cT1-T2a and Gleason score  $\leq 6$  and prostate specific antigen (PSA)  $< 10\mu\text{g/L}$ .
  - **Intermediate-risk:** cT2b-T2c or Gleason score = 7 or PSA  $10\text{--}20\mu\text{g/L}$ .
  - **High-risk:** cT3a, Gleason score 8-10 or PSA  $> 20\mu\text{g/L}$ .
  - **Very-high-risk:** cT3b-T4 or any T, N1. **(C)**

#### Radiology and diagnosis

- 2.3.1.1** A suspect digital rectal examination is usually an indication for prostate biopsy which commonly involves needle biopsy in conjunction with transrectal ultrasound, regardless of PSA level. **(B)**
- 2.3.2.1** In patients with persistent clinical concern for prostate cancer following at least one negative prior prostate biopsy, consider multiparametric MRI with a view to targeted biopsy if appropriate. **(B)**
- 2.3.3.1** Consider multiparametric MRI if knowledge of the T or N stage could affect management. **(C)**
- 2.3.4.1** CT may be considered for the staging of men with high-risk prostate cancer when the PSA is  $> 20\mu\text{g/L}$  or when locally advanced or when the Gleason score is  $\geq 8$ . **(C)**
- 2.3.5.1** An isotope bone scan is recommended for patients with prostate cancer with a Gleason score  $\geq 8$ , PSA  $> 20\mu\text{g/L}$  or stage  $\geq \text{T3}$ , regardless of serum PSA. **(B)**
- 2.3.6.1** All patients with prostate cancer with an abnormality identified on planar scintigraphic imaging in the lumbosacral spine, pelvis or upper femora should have a SPECT scan, where available. **(C)**
- 2.3.7.1** There is no reliable evidence to support the routine use of  $^{18}\text{F}$ -Fluorocholine/ $^{11}\text{C}$ -Choline imaging in patients with prostate cancer at present. **(C)**
- 2.3.8.1** A prostate biopsy of 10-12 cores is recommended. **(C)**

#### Pathology

- 2.4.1.1** A report should be generated for each designated site of biopsy. **(C)**
- 2.4.1.2** A maximum of three cores should be submitted per cassette. **(D)**
- 2.4.1.3** To optimise the detection of small lesions, blocks should be cut and examined at three levels. **(C)**
- 2.4.2.1** For determining tumour extent in prostate core biopsies, when there are multiple foci of prostate cancer in a single core separated by benign intervening stroma, it is suggested that the collapsing method is used (i.e. where intervening benign tissue is excluded from the measurement). **(D)**
- 2.4.3.1** For each biopsy site the presence of biopsies positive for carcinoma and the ISUP 2005 Gleason score should be reported. The pathologists should assign a separate Gleason score to each sample core (or site) rather than an overall score for the entire biopsy session. **(C)**
- 2.4.3.2** Depending on clinical practice, it may be useful to provide an overall Gleason score to the case, in addition to site specific Gleason scores. **(D)**

- 2.4.4.1** The extent of cancer involvement in a core biopsy should be reported. This may be done in millimetres or percentage involvement. **(B)**
- 2.4.5.1** All prostate core biopsies should be reported with the pathological prognostic factors as outlined in Table 2. **(B)**
- 2.4.6.1** All radical prostatectomy specimens should be reported with the minimum dataset items as outlined in Table 3. **(B)**
- 2.4.7.1** Positive surgical margins are defined by microscopic tumour in touch with ink. **(B)**
- 2.4.7.2** A margin status is negative if tumour is very close to the inked surface of the margin or when they are at the surface of the tissue lacking any ink. **(B)**
- 2.4.8.1** It is optional, according to local practice, to report extent of margin positivity. This can be done either as mm of involvement or by documenting focal versus extensive involvement. **(B)**
- 2.4.9.1** The location of positive margins should be reported. Locations may be noted as follows: left or right and posterior, posterolateral, lateral, or anterior at either the apex, mid, or base (or bladder neck). **(D)**
- 2.4.10.1** Extraprostatic extension should be documented. **(B)**
- 2.4.10.2** Extraprostatic extension should be quantified. The method of quantification should be according to local practice. **(B)**
- 2.4.12.1** If it is possible to identify a dominant tumour nodule in an anterior location then this should be documented. There is less definitive evidence at this time to specify peripheral versus transitional location. **(D)**
- 2.4.13.1** The reporting of pT2 substage (a, b, and c) is optional as it has not been proven to be of prognostic significance. **(B)**
- 2.4.14.1** There is insufficient evidence regarding the additional prognostic value of tumour volume to recommend mandatory reporting of prostate cancer volume. **(B)**
- 2.4.14.2** It may be recommended to assess the greatest dimension of the dominant tumour nodule, if identified, or to provide a rough estimate of the percentage of cancer tissue in the prostate. **(D)**

### Active surveillance

- 2.5.1.1** Active surveillance is an option for men with the lowest risk of prostate cancer progression for whom radical treatment is suitable. **(C)**
- Definition for lowest risk for prostate cancer progression:**  
cT1c, PSA <10µg/L, biopsy Gleason score ≤6 (at least 12 cores), ≤2 positive cores, minimal biopsy core involvement (<50% cancer per biopsy).
- 2.5.2.1** The protocol in Figure 2 is recommended for men who have chosen active surveillance. **(D)**
- 2.5.3.1** Prior to enrolment in an active surveillance programme, a multiparametric MRI scan should be performed. **(B)**
- 2.5.4.1** Given the evidence available from large centre trials, ≤2 positive cores and a maximum of 50% involvement of one core is recommended. **(B)**
- 2.5.5.1** A repeat prostate biopsy is mandatory for all patients considering active surveillance and this can be done by either the transrectal or transperineal approach. **(B)**
- 2.5.5.2** There is emerging evidence that transperineal biopsies identify more clinically important prostate cancer. **(C)**
- 2.5.6.1** Criteria for conversion to active treatment include:
- o Change in PSA
  - o Change in DRE findings
  - o Upgrade of disease (including increase in core volume, increase in number of positive cores and increase in Gleason grade)
  - o MRI findings suggestive of disease progression
  - o Patient preference for radical treatment. **(D)**

### Surgery

- 2.6.1.1** Radical treatment may be an option for men with low-risk prostate cancer and life expectancy of ≥10 years. **(C)**
- 2.6.1.2** If radical treatment is being provided, then radical prostatectomy is a treatment option for men with low-risk prostate cancer. **(B)**

- 2.6.2.1 Radical treatment is recommended for men with intermediate-risk prostate cancer with a life expectancy of  $\geq 10$  years. **(B)**
- 2.6.2.2 Radical prostatectomy is a treatment option for men with intermediate-risk prostate cancer with a life expectancy of  $\geq 10$  years. **(B)**
- 2.6.3.1 Radical prostatectomy may be considered as a treatment option in high-risk disease, either alone or in combination with other therapies. **(C)**
- 2.6.4.1 A lymph node dissection is **not** necessary in low-risk, localised prostate cancer, because the risk for positive lymph nodes does not exceed 5%. **(B)**
- 2.6.4.2 Extended lymph node dissection should be performed in intermediate-risk, localised prostate cancer if the estimated risk for positive lymph nodes exceeds 5%, using an available nomogram. **(B)**
- 2.6.4.3 Extended lymph node dissection should be performed in high-risk cases. In these circumstances, the estimated risk for positive lymph nodes is 15%-40%. **(B)**

## Medical oncology

- 2.7.1.1 The evidence that favours immediate hormone therapy over delayed therapy is not convincing. Therefore, this choice should be made on an individual basis for each patient. Relevant factors include patient preference, the presence of symptoms (i.e. pain), the extent of metastases, PSADT, age, comorbidity, and the effect of treatment on quality of life. **(C)**
- 2.7.2.1 For patients with biochemical relapse or metastatic recurrence continuous androgen deprivation therapy is the standard option. **(B)**
- 2.7.2.2 Intermittent androgen deprivation therapy can be considered an acceptable alternative option to be discussed with patients. **(B)**
- 2.7.3.1 Androgen deprivation therapy should be continued indefinitely in these patients. **(D)**
- 2.7.4.1 For men with castration resistant prostate cancer, second line hormone therapy should be considered. **(A)**
- 2.7.4.2 For men with castration resistant prostate cancer in whom chemotherapy is **not** yet clinically indicated, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide. **(A)**
- 2.7.4.3 For men with castration resistant prostate cancer, whose disease has progressed on or after a docetaxel-based chemotherapy regimen, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide. **(A)**
- 2.7.5.1 Clinicians should offer treatment with abiraterone (+ prednisone), cabazitaxel or enzalutamide to patients with metastatic castration resistant prostate cancer with good performance status who have received prior docetaxel chemotherapy. **(A)**
- 2.7.5.2 Abiraterone (+ prednisone) or enzalutamide may also be considered in patients who have **not** received docetaxel. **(A)**
- 2.7.5.3 Patients with metastatic castration resistant prostate cancer who have predominantly bone metastases may benefit from radium-223. **(A)**
- 2.7.6.1 For men with castration resistant prostate cancer and bone metastases, treatment with zoledronic acid should be considered. Consider denosumab for men in whom zoledronic acid is contraindicated or not tolerated. **(B)**

## Radiation oncology

### Patients with undetectable PSA post-operatively

- 2.8.1.1 Patients who are classified as margin positive or with seminal vesicle involvement after radical prostatectomy, should be considered for adjuvant radiotherapy. **(A)**
- 2.8.1.2 Patients who are classified as margin negative and who have no other adverse prognostic features should be monitored, pending the results of ongoing clinical trials (e.g. RADICALS, RAVES, GETUG), with early salvage radiotherapy when PSA becomes detectable using ultra-sensitive PSA assay. **(A)**

### Patients with detectable PSA post-operatively

- 2.8.1.3 Salvage radiotherapy is recommended for patients who develop a detectable PSA, in the absence of metastatic disease. **(B)**

**The role of external beam radiotherapy (EBRT) and/or brachytherapy in:****Low-Risk Prostate Cancer**

**2.8.2.1** All radiotherapy treatment options are appropriate (EBRT and/or brachytherapy) to be considered for patients with low-risk prostate cancer. **(B)**

**Intermediate-Risk Prostate Cancer**

**2.8.2.2** All radiotherapy treatment options are appropriate (EBRT and/or brachytherapy) to be considered for patients with intermediate-risk prostate cancer. **(B)**

**2.8.2.3** Hormonal therapy should be considered in addition to EBRT. **(A)**

**High-Risk Prostate Cancer**

**2.8.2.4** Radiotherapy treatment options for patients with high-risk prostate cancer are EBRT in combination with hormonal therapy; EBRT and brachytherapy combinations; EBRT in combination with brachytherapy and hormonal therapy. **(B)**

**Very-High-Risk Prostate Cancer**

**2.8.2.5** A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients. **(A)**

**2.8.2.6** A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients. **(C)**

**Biochemical recurrence following curative treatment**

**2.8.3.1** Following radical prostatectomy, a recurrence of prostate cancer can be defined as at least two PSA readings  $\geq 0.2\mu\text{g/L}$ . **(C)**

**2.8.3.2** Following radiotherapy, a recurrence of prostate cancer can be defined as a PSA value of  $2\mu\text{g/L}$  above the nadir after treatment. **(C)**

**The role of hormone therapy in conjunction with radiotherapy in:****Low-Risk Prostate Cancer**

**2.8.5.1** There is a lack of evidence to suggest that the addition of androgen deprivation therapy to radical radiotherapy is of benefit in patients with low-risk disease. **(C)**

**Intermediate-Risk Prostate Cancer**

**2.8.5.2** Androgen deprivation therapy for four to six months should be considered in conjunction with EBRT. A pooled analysis suggests that a duration of six months is optimal. **(A)**

**High-Risk Prostate Cancer**

**2.8.5.3** A combination of radiation therapy and consideration for long term hormone androgen deprivation therapy. **(A)**

**2.8.5.4** EBRT plus brachytherapy with or without androgen deprivation therapy. **(C)**

**Very-High-Risk Prostate Cancer**

**2.8.5.5** A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients. **(A)**

**2.8.5.6** A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients. **(C)**

**Palliative Care**

**2.9.1.1** For patients with cancer, early provision of palliative care can improve patient outcomes. **(C)**

**2.9.1.2** Assessment of palliative care needs should be an ongoing process throughout the course of a patient's cancer illness and services provided on the basis of identified need. **(D)**

**Good practice points**

Recommended best practice based on the clinical experience of the Guideline Development Group.

## 2.2 Defining Risk Categories

### Clinical question 2.2.1

What are the definitions for the following categories of prostate cancer:

- **Low-risk prostate cancer**
- **Intermediate-risk prostate cancer**
- **High-risk prostate cancer**
- **Very-high-risk prostate cancer?**

#### Evidence statement

The current EAU guideline (Mottet et al., 2014) and a retrospective cohort study (D'Amico et al., 1998) addressed this question.

Prostate Specific Antigen (PSA), Gleason score and tumour stage are predictive of cancer outcome (D'Amico et al., 1998).

**Low-risk:** cT1-T2a and Gleason score  $\leq 6$  and PSA  $< 10\mu\text{g/L}$  (Mottet et al., 2014).

**Intermediate-risk:** cT2b-T2c or Gleason score = 7 or PSA  $10\text{--}20\mu\text{g/L}$  (Mottet et al., 2014).

**High-risk:** cT3a Gleason score 8-10 or PSA  $> 20\mu\text{g/L}$  (Mottet et al., 2014).

**Very-high-risk:** cT3b-T4 N0 or any T, N1 (Mottet et al., 2014).

Other disease classification systems are emerging, e.g. CAPRA. However, the D'Amico classification system is currently the gold standard. This will remain under review as new evidence emerges.

Recommendation 2.2.1.1	Grade
It is recommended that the risk categories stated are used when interpreting and placing patients into risk groups.	C

#### Good practice point

Prior to considering treatment, clinicians need to take into account individual co-morbidities, age, and life expectancy. All patients should be discussed at an multidisciplinary meeting and patients should be seen in consultation by both a urologist and a radiation oncologist.

## 2.3 Radiology and Diagnosis

### **Responsibility for the implementation of recommendations**

While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.



**Clinical question 2.3.1****What is the clinical importance of an abnormal prostate on Digital Rectal Examination (DRE)?****Evidence statement**

Current guidelines from the EAU (Mottet et al., 2014) and NICE (2014) addressed this question.

Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is about 0.2mL or larger. In about 18% of patients, prostate cancer is detected by a suspect DRE alone, irrespective of the PSA level (Richie et al., 1993). A suspect DRE in patients with a PSA level of up to 2µg/L has a positive predictive value of 5%-30% (Carvalhal et al., 1999). A suspect DRE is a strong indication for prostate biopsy as it is predictive for more aggressive (Gleason score  $\geq 7$ ) prostate cancer (Okotie et al., 2007, Gosselaar et al., 2008). (Mottet et al., 2014)

DRE procedures are very common, but information on this is not routinely collected. (NICE, 2014)

Radiological screening, including computed tomography (CT) and magnetic resonance imaging (MRI) are also often used to aid diagnosis and staging. (NICE, 2014)

<b>Recommendation 2.3.1.1</b>	<b>Grade</b>
A suspect digital rectal examination is usually an indication for prostate biopsy which commonly involves needle biopsy in conjunction with transrectal ultrasound, regardless of PSA level.	<b>B</b>

**Clinical question 2.3.2**

**Is MRI recommended for diagnosing prostate cancer in men with an elevated PSA and repeated negative TRUS biopsies?**

**Evidence statement**

Current guidelines from the European Society of Urogenital Radiology (ESUR) (Barentsz et al., 2012), a prospective randomised controlled trial (RCT) (Panebianco et al., 2010), a retrospective cohort study (Hoeks et al., 2012) and a review (Lawrentschuk and Fleshner, 2009) addressed this question.

Based on the above literature a considerable number of clinically significant occult prostate cancers with previous negative biopsy are identified (approx. 40%) using multiparametric MRI and subsequent targeted biopsies.

Although all studies had small numbers and variable imaging and biopsy techniques they showed consistent results.

<b>Recommendation 2.3.2.1</b>	<b>Grade</b>
In patients with persistent clinical concern for prostate cancer following at least one negative prior prostate biopsy, consider multiparametric MRI with a view to targeted biopsy if appropriate.	<b>B</b>

**Clinical question 2.3.3****Which patients with prostate cancer should have an MRI for staging?****Evidence statement**

Current guidelines from the EAU (Mottet et al., 2014) and NICE (2014) addressed this question. However, there is a lack of consensus elucidating which patient groups should have an MRI for staging.

MRI is now the most commonly used imaging technique for T-staging men with prostate cancer. (NICE, 2014)

The accuracy of staging of the disease may be improved by MRI which can reduce unnecessary treatment-related morbidity when there is no possibility of cure (Sanchez-Chapado et al., 1997, Bates et al., 1997). Multiparametric MRI may add additional information and can help to gauge suitability for active surveillance or feasibility of nerve-sparing surgery in low-risk patients. In intermediate-risk patients it can aid in identifying stage T3 disease, while in high-risk patients an MRI of the spine may detect the degree of metastases. (NICE, 2014)

The use of the endorectal coil improves staging accuracy at 1.5T, as shown by two studies that found accuracies of 77%-83% for combined endorectal and external coils versus 59%-68% for external coils alone (Futterer et al., 2007, Hricak et al., 1994). Dynamic contrast-enhanced imaging used in combination with T2-weighted imaging may also improve local staging, at least for less-experienced readers (Futterer et al., 2005, Bloch et al., 2007). The high-field strength allows high-resolution T2-weighted imaging (Futterer et al., 2004) and results obtained at 3T seem better than those obtained at 1.5T (Heijmink et al., 2007, Futterer et al., 2006). Even if MRI performances in local staging are not perfect, it may improve the prediction of the pathological stage when combined with clinical data (Wang et al., 2004, Poulakis et al., 2004). (Mottet et al., 2014)

Given its low sensitivity to microscopic invasion, MRI is not recommended in the local staging of low-risk patients but MRI may be useful in selected patients with intermediate- to high-risk cancers (Wang et al., 2004, D'Amico et al., 2000, Engelbrecht et al., 2001). (Mottet et al., 2014)

Images may be optimised with use of endorectal coil and 3T magnet strength but there would be implications for routine use.

<b>Recommendation 2.3.3.1</b>	<b>Grade</b>
Consider multiparametric MRI if knowledge of the T or N stage could affect management.	<b>C</b>

**Clinical question 2.3.4****What is the role of CT scan for diagnosis and staging of prostate cancer?****Evidence statement**

The current AUA (2013) guideline addressed this question.

CT may be considered for the staging of men with high-risk prostate cancer when the PSA is greater than 20µg/L or when locally advanced or when the Gleason score is ≥8. Although this is international expert opinion, supporting data are lacking. CT identification of pelvic adenopathy depends upon lymph node enlargement, and the correlation between nodal size and metastatic involvement is poor. (AUA, 2013)

<b>Recommendation 2.3.4.1</b>	<b>Grade</b>
CT may be considered for the staging of men with high-risk prostate cancer when the PSA is >20µg/L or when locally advanced or when the Gleason score is ≥8.	<b>C</b>

**Clinical question 2.3.5****Which men with prostate cancer should have an isotope bone scan?****Evidence statement**

Guidelines from the AUA (2013) and Oncoline (2007) addressed this question.

A systematic review by Abuzallouf et al., (2004) described the pooled results of 23 clinical studies on the predictive value of skeletal scintigraphy in patients with a primary diagnosis of prostate cancer. A total of 8,644 patients were assessed, and bone metastases were found in 1,453 patients. When analysed according to PSA level, bone metastases were found in 2.3%, 5.3%, and 16.2% of patients with PSA levels of <10, 10.1-19.9, and 20-49.9µg/L, respectively. When analysed according to clinical tumour stage, bone metastases were found in 6.4% of men with localised prostate cancer and in 49.5% of men with locally advanced disease. When analysed by Gleason score, bone metastases were found in 5.6% of those with a Gleason score of ≤7 and in 29.9% of those with a Gleason score 8-10. (Oncoline, 2007)

Bone scans are generally not necessary in patients with newly diagnosed prostate cancer who have a PSA <20µg/L unless the history or clinical examination suggests bony involvement. Metastatic disease is significantly more common in advanced local disease or in high-grade disease, and it is reasonable to consider bone scans when the patient has a Gleason score of ≥8, or stage ≥T3 prostate cancer, even if the PSA is <10µg/L (Ries et al., 2008, Abuzallouf et al., 2004). (AUA, 2013)

<b>Recommendation 2.3.5.1</b>	<b>Grade</b>
An isotope bone scan is recommended for patients with prostate cancer with a Gleason score ≥8, PSA >20µg/L or stage ≥T3, regardless of serum PSA.	<b>B</b>

### Clinical question 2.3.6

#### What is the role of the conventional isotope bone scan versus SPECT-CT in diagnosing bone metastases?

##### Evidence statement

A prospective study (Giovanella et al., 2011) and a review (Langsteger et al., 2012) addressed this question.

The primary aim of scintigraphic assessment in patients with prostate cancer is to detect or exclude the presence of bone metastases as early as possible (Thurairaja et al., 2004). A prospective study of 194 patients (Giovanella et al., 2011) found bone single photon emission computed tomography (SPECT) to be more sensitive than whole-body bone scintigraphy (WBS), as reflected by its detection of 13 metastases missed by WBS alone. Identification of malignant bone involvement by SPECT (but not WBS) led to modification of the case management in six patients. The superiority of bone SPECT over WBS in detecting bone metastases was previously reported (Sarıkaya et al., 2001). Previous studies have generally tended to use a single SPECT view, providing tomographic data for a limited skeletal region, whereas few patients have been submitted to several SPECT views with prolonged acquisition protocols (Even-Sapir et al., 2006). (Giovanella et al., 2011)

Images in this study were processed with an iterative algorithm rather than standard filtered back-projection, as this algorithm provides better noise properties and higher contrast and resolution (Song et al., 2005, Schünemann et al., 2006, Wells et al., 2004). Patient-based analysis showed that the sensitivity and positive predictive value (PPV) increased from 79%-87% and 83%-78% on WBS to 90%-95% and 93%-98% on multi-field-of-view single photon emission tomography (multi-FOV SPECT), without any reduction in specificity. (Giovanella et al., 2011)

<sup>99m</sup>Tc-oxidronate (<sup>99m</sup>Tc-HDP) multi-FOV SPECT was found to be a sensitive and specific tool for detecting bone metastases in patients with prostate cancer and to perform better than WBS examination in this clinical field. The data suggest that multi-FOV SPECT could play an important role in the assessment of patients with prostate cancer, especially when PSA levels are below 40µg/L. The specificity of bone SPECT is likely to improve further with the introduction of SPECT-CT techniques into clinical practice. (Giovanella et al., 2011)

The addition of a SPECT to planar bone scanning has improved the diagnostic accuracy of this modality (Even-Sapir, 2005). SPECT provides precise localisation of abnormal findings and allows better differentiation between benign and malignant lesions located on complex structures especially in the vertebral column hence improving the specificity of this modality (Even-Sapir et al., 1993, Savelli et al., 2001). Additionally, SPECT (in comparison with planar bone scintigraphy) can detect 20%-50% more vertebral lesions thus improving also the sensitivity and providing a negative predictive value of 98% for the assessment of suspicious vertebral lesions (Savelli et al., 2001, Gates, 1998, Han et al., 1998). (Langsteger et al., 2012)

The reported sensitivity and specificity of bone SPECT for diagnosis of bone metastases are 87%-92% and 91%-93%, respectively (Hamaoka et al., 2004, Ben-Haim and Israel, 2009, Savelli et al., 2001). Nakai et al., (2005) reported in a retrospective study of 89 patients a sensitivity, specificity and accuracy of 78%, 82% and 80% respectively when using bone SPECT in the detection of bone metastases. In addition, the recent development of whole body SPECT protocols provide tomographic examination of the entire skeleton within an acceptable acquisition time and subsequent improvement in sensitivity (Even-Sapir et al., 2007). (Langsteger et al., 2012)

Recommendation 2.3.6.1	Grade
All patients with prostate cancer with an abnormality identified on planar scintigraphic imaging in the lumbosacral spine, pelvis or upper femora should have a SPECT scan, where available.	C

**Clinical question 2.3.7****What is the role of <sup>18</sup>F-Fluorocholine/<sup>11</sup>C-Choline imaging in the diagnosis of prostate cancer?****Evidence statement**

A systematic review and meta-analysis (Umbehr et al., 2013) and a study of diagnostic accuracy (Afshar-Oromieh et al., 2013) addressed this question.

Positron emission tomography (PET) and positron emission tomography-computed tomography (PET-CT) using <sup>11</sup>C-choline or <sup>18</sup>F-Fluorocholine (<sup>18</sup>F-FCH) as tracers cannot be recommended for routine use in prostate cancer imaging. Overall, the diagnostic evidence seems to be higher in restaging settings than in staging settings. However, careful selection of eligible patients seems to be the most important issue to avoid false negative results up front in staging as well as restaging settings. In general, the meaningful use of these imaging modalities seems to be restricted to high-risk patients, and previously described clinical factors (Richter et al., 2010, Picchio et al., 2011, Giovacchini et al., 2010a, Giovacchini et al., 2010b, Castellucci et al., 2009) should be considered in patient selection. (Umbehr et al., 2013)

In staging settings, mainly high-risk Gleason scores (8–10) and high PSA levels ( $\geq 20\mu\text{g/L}$ ) seem to be predictive (Kjölhede et al., 2012), whereas in restaging settings, minimal recurrent PSA levels ( $\geq 1\mu\text{g/L}$ ), short PSA doubling time ( $< 3$  months to a maximum of 6 months), and initial tumour stage ( $\geq \text{pT3b}$  or  $\text{pN1}$ ) should be considered (Picchio et al., 2011, Murphy et al., 2011). (Umbehr et al., 2013)

Although the available evidence indicates that choline PET has analytic validity in subsets of patients, proof of clinical validity and, ultimately, clinical utility still must be provided. (Umbehr et al., 2013)

There is also emerging evidence for the use of PET imaging with a [<sup>68</sup>Ga] gallium-labelled prostate-specific membrane antigen (PSMA) ligand in the diagnosis of prostate cancer (Afshar-Oromieh et al., 2013).

<b>Recommendation 2.3.7.1</b>	<b>Grade</b>
There is no reliable evidence to support the routine use of <sup>18</sup> F-Fluorocholine/ <sup>11</sup> C-Choline imaging in patients with prostate cancer at present.	<b>C</b>

**Clinical question 2.3.8**

**What is the optimum number of cores that should be taken in prostate biopsies for the diagnosis and staging of prostate cancer?**

**Evidence statement**

The current guideline NICE (2014) guideline and a systematic review (Eichler et al., 2006) addressed this question.

Eichler et al., (2006) concluded that prostate biopsy schemes consisting of 12 cores that add laterally directed cores to the standard sextant scheme strike the balance between the cancer detection rate and adverse events. Taking more than 12 cores added no significant benefit.

Cormio et al., (2014) found no significant difference in the detection rate of 10-, 14- or 18-core schemes (39%, 42% and 42% respectively), however, there was a significant difference between these and a 6-core scheme (33% detection rate). Standard agreed practice in the UK is to take 10-12 cores. (NICE, 2014)

<b>Recommendation 2.3.8.1</b>	<b>Grade</b>
A prostate biopsy of 10-12 cores is recommended.	<b>C</b>



## 2.4 Pathology

### **Responsibility for the implementation of recommendations**

While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

**Clinical question 2.4.1****What is the optimum handling, processing, and reporting of prostate core biopsies?****Evidence statement**

Current guidelines from the EAU (Mottet et al., 2014), Oncoline (2007), PCRMP (2006), RCPATH (2006) and a review (Fine et al., 2012) addressed this question.

There is consistency in international guidelines regarding the handling, processing, and reporting of prostate core biopsies (Mottet et al., 2014, Oncoline, 2007, RCPATH, 2009). When prostate cores are submitted separately or assigned a clear site designation by container, the pathology report should reflect this (Fine et al., 2012).

As a minimum requirement, cores should be identifiable according to the side (right/left) of the gland that they originated from. This information is of paramount importance as it may enable a unilateral nerve sparing prostatectomy to be performed when a cancer involves only one side of the gland. (PCRMP, 2006)

In addition, a number of studies have correlated the presence and amount of cancer in different regions with risk of higher pathologic stage and margin positivity (Zhou and Epstein, 2003). (Fine et al., 2012)

To achieve optimal flattening and alignment of individual cores, one should embed a maximum of three cores per cassette and use sponges or paper to keep the cores stretched and flat (Van der Kwast et al., 2003, Rogatsch et al., 2000). To optimise the detection of small lesions, blocks should be cut at three levels (Pelzer et al., 2005). It is helpful to mount intervening tissue sections in case additional immunostaining is needed. (Mottet et al., 2014)

<b>Recommendation 2.4.1.1</b>	<b>Grade</b>
A report should be generated for each designated site of biopsy.	<b>C</b>
<b>Recommendation 2.4.1.2</b>	<b>Grade</b>
A maximum of three cores should be submitted per cassette.	<b>D</b>
<b>Recommendation 2.4.1.3</b>	<b>Grade</b>
To optimise the detection of small lesions, blocks should be cut and examined at three levels.	<b>C</b>

**Good practice point**

Intervening spare sections should be cut and retained at each of three levels per block.

**Clinical question 2.4.2****What is the best method of determining percentage core involvement or tumour length in prostate biopsies?****Evidence statement**

Two retrospective studies (Brimo et al., 2008, Karram et al., 2011) addressed this question.

There is no consensus as to the optimal method of measuring tumour length or percentage core involvement, especially when there are two or more foci of prostate cancer in a single core separated by benign intervening stroma (Karram et al., 2011). Discontinuous foci can be measured as if there were a single continuous focus, i.e. measure from the start of one focus to the end of the last focus (end-to-end method) or they can be measured as individual foci and each focus added together excluding the areas of intervening benign tissue (collapsed method). Both methods are almost equally commonly used (Egevad et al., 2006).

Karram et al., (2011) suggests that including benign prostate tissue in the measurement is more predictive of stage and margins than ignoring the intervening benign tissue.

Brimo et al., (2008) suggests the prognostic significance of estimating cancer lengths may not differ whether one considers separate foci of cancer on a single core as separate or as one focus, as long as the intervening stroma is  $\leq 5$ mm.

For the benefit of uniformity and data collection, it is suggested by the GDG that the collapsed method be used. When multiple foci of carcinoma are separated by intervening benign prostatic glands and stroma, pathologists will collapse the tumour by disregarding the intervening benign prostate tissue (Brimo et al., 2008). (Fine et al., 2012)

It is not possible to draw a definitive conclusion at this time.

<b>Recommendation 2.4.2.1</b>	<b>Grade</b>
For determining tumour extent in prostate core biopsies, when there are multiple foci of prostate cancer in a single core separated by benign intervening stroma, it is suggested that the collapsing method is used (i.e. where intervening benign tissue is excluded from the measurement).	<b>D</b>

**Clinical question 2.4.3****How should Gleason score be calculated and reported in prostate core biopsies?****Evidence statement**

Current guidelines from the EAU (Mottet et al., 2014), RCPATH (2009) and a review (Fine et al., 2012) addressed this question.

The International Society of Urological Pathology (ISUP) 2005 modified Gleason Score should be reported (Mottet et al., 2014, RCPATH, 2009).

There are certain circumstances in which reporting primary plus secondary Gleason grades may be inexact, as the traditional Gleason Score is unlikely to be representative of cancer in the gland (Table 5). (Fine et al., 2012)

The pathologist should assign a separate Gleason Score to each sampled core (or site), rather than an overall score for the entire biopsy session (Epstein et al., 2005a, Rubin et al., 2004, Kunju et al., 2009). (Fine et al., 2012)

**Table 5** Reporting recommendations for special Gleason grading scenarios

Clinical setting	Recommendation
Only one grade present (e.g. GG 3)	This grade is doubled (GS 3+3 = 6)
Abundant high-grade cancer (e.g. GG 4) with <5% lower-grade cancer	The lower grade cancer is ignored (GS 4+4 = 8)
Smaller focus with mostly GG 4 and few glands of GG 3	Since GG 3 occupies >5%, the lower grade cancer will be included (GS 4 + 3 = 7)
Abundant GG 3 with any extent of GG 4	The higher grade will be included (GS 3+4 = 7)
Three grades (e.g. GG 3, 4, and 5) present	Classify as high grade (assign most common plus highest grade)
NB: Multiple cores showing different grades – cores submitted separately and/or with designated location	Each core or site will be assigned a separate GS
NB: Multiple cores showing different grades – all cores were submitted in one container or cores are fragmented	An overall GS will be assigned to the specimen
GG = Gleason grade, GS = Gleason score, NB = Needle biopsy	

Adapted from Fine et al., (2012)

ISUP recommends assigning a Gleason score to every 'specimen' but recognises the difficulties particularly if multiple biopsies are submitted in a single cassette and have fragmented. However, it also gives the option of creating a 'global' or composite Gleason score for the case. It defers to the clinician whether the global Gleason score or the 'highest' Gleason score should be used. Discordance between composite and highest Gleason scores is relatively infrequent, and usually occurs because one core contains only high grade Gleason (e.g. 4+4) whereas all the other cores contain a lower grade (e.g. 3+4). (RCPATH, 2009)

Depending on clinical practice, it may be useful to provide an overall Gleason score to the case, in addition to site specific Gleason scores.

Individual Gleason scores should be assigned to each individual site. If multiple cores are submitted per site, it may be useful to highlight the presence of a higher Gleason score if this is present in an individual core. Similarly, the extent of the most involved core per site can be given.

<b>Recommendation 2.4.3.1</b>	<b>Grade</b>
For each biopsy site, the presence of biopsies positive for carcinoma and the ISUP 2005 Gleason score should be reported. The pathologists should assign a separate Gleason score to each sample core (or site) rather than an overall score for the entire biopsy session.	<b>C</b>

<b>Recommendation 2.4.3.2</b>	<b>Grade</b>
Depending on clinical practice, it may be useful to provide an overall Gleason score to the case, in addition to site specific Gleason scores.	<b>D</b>

**Clinical question 2.4.4****Should extent of cancer in a prostate biopsy core be measured in millimetres (mm) or percent?****Evidence statement**

Guidelines from the EAU (Mottet et al., 2014), Oncoline (2007), RCPATH (2009) and a review (Fine et al., 2012) addressed this question.

The international guidelines are consistent that extent of cancer (either mm or percent) should be reported.

There is a potential clinical impact of reporting the extent of cancer in a prostate core biopsy, because of the size criteria, >50% or >5mm might trigger treatment versus active surveillance.

There are numerous studies which have addressed this topic and there is equal evidence to suggest that the extent of cancer in a core biopsy may be measured in either mm or percentage involvement (Mottet et al., 2014, Oncoline, 2007, RCPATH, 2009, Fine et al., 2012).

<b>Recommendation 2.4.4.1</b>	<b>Grade</b>
The extent of cancer involvement in a core biopsy should be reported. This may be done in millimetres or percentage involvement.	<b>B</b>

**Clinical question 2.4.5**

**For men who have had a prostate biopsy, what are the pathological prognostic factors?**

**Evidence statement**

The CAP (2012) guideline and a review (Fine et al., 2012) addressed this question.

The literature is largely in agreement on pathological prognostic factors (Table 6), which include Gleason score, number of positive cores and tumour quantification (CAP, 2012, Fine et al., 2012).

**Table 6** Pathological prognostic factors

<b>Ideally the following clinical data would be provided:</b>
PSA Clinical stage (DRE) Number of prostatic biopsies Side +/- site of prostatic biopsies History of previous treatment History of previous biopsies Imaging findings (if any)
<b>Macroscopic pathology data (per site submitted):</b>
Number of cores or fragments Length of cores
<b>Microscopic pathology data:</b>
Modified Gleason score Number of positive cores per site Total percentage/mm of cancer per site Perineural invasion, if present Seminal vesicle invasion, if present Vascular invasion, if present Involvement of adipose tissue if present If no carcinoma is present, any features that should lead to consideration of re-biopsy, including: <ul style="list-style-type: none"> <li>– High grade prostatic intraepithelial neoplasia</li> <li>– Foci suspicious for but not diagnostic of carcinoma</li> </ul>
<b>Others features which could be reported:</b>
Presence of rectal mucosa (optional) Presence of inflammation (optional)

<b>Recommendation 2.4.5.1</b>	<b>Grade</b>
All prostate core biopsies should be reported with the pathological prognostic factors as outlined in Table 2.	<b>B</b>

**Good practice point**  
 Pathologists reporting prostate biopsies should participate in external quality assurance programmes.

**Clinical question 2.4.6****For men who have had a radical prostatectomy what are the essential reporting items?****Evidence statement**

The current EAU guideline (Mottet et al., 2014) addressed this question.

There is a large body of consistent evidence in the international guidelines, on reporting items for radical prostatectomy.

**Radical prostatectomy specimen report**

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (see Table 7) (Mottet et al., 2014).

**Minimum dataset for reporting radical prostatectomy specimens**

- Typing (>95% of prostate cancer represents conventional (acinar) adenocarcinoma)
- Grading according to the modified Gleason score

**(Sub) Staging and surgical margin of the tumour**

- If appropriate, location and extent of extraprostatic extension, location and extent of positive surgical margins, presence of bladder neck invasion, laterality of extraprostatic extension or seminal vesicle invasion.
- Additional information may be provided on multifocality, diameter of the dominant tumour and zonal location (transition zone, peripheral zone, anterior zone) of the dominant tumour.

As a result of the complex information provided on each radical prostatectomy specimen, the use of synoptic (-like) or checklist reporting is recommended. (Mottet et al., 2014)

**Table 7** Example reporting proforma of radical prostatectomy

Macroscopy	
<b>Weight of prostate:</b>	____ g (indicate if weight is with or without seminal vesicles)
<b>Dimensions of prostate:</b>	____ mm apex-base, ____ mm anterior-posterior, ____ mm lateral
<b>External Surface:</b>	Description (i.e. smooth, incisions, etc) _____
<b>Visible tumour:</b>	location(s) _____ dimension(s) _____
<b>Seminal Vesicles:</b>	Right, dimensions ____ x ____ x ____ mm, vas ____ mm Left, dimensions ____ x ____ x ____ mm, vas ____ mm
<b>Lymph Nodes:</b>	Measurement of lymph node packet, right and left (optional) Right: ____ Indicate number of lymph nodes identified grossly Left: ____ Indicate number of lymph nodes identified grossly
	Approximate volume of gland embedded: 100% /75-99% / 50-74% etc.
	Tissue withheld for bio banking: Yes/No



<b>Microscopy</b>	
Tumour type: <b>Acinar / Other (specify)</b> _____ / no tumour	
Gleason Grade:	<b>Primary</b> _____ <b>Secondary</b> _____ <b>Sum score</b> _____ <b>(Primary plus secondary)</b> <b>Tertiary</b> _____
Tumour volume/size (optional): _____ (indicate either approximate tumour volume or size of largest tumour nodule)	
Location (size, zone) of dominant tumour nodule _____	
<b>Stage:</b> as follows; pT2 sub staging is optional	
$\leq 1/2$ of one lobe involved – pT2a $> 1/2$ of one lobe involved – pT2b Both lobes involved – pT2c pT3 Extraprostatic extension: indicate if p3a extraprostatic extension, without seminal vesicle involvement pT3b seminal vesicle involvement Site(s) of extraprostatic extension _____ Extent of extraprostatic extension (focal vs. non-focal or mm of involvement)*: _____ (Note: microscopic bladder neck invasion constitutes pT3a disease) pT4 Tumour involving adjacent organs or pelvic wall _____ (indicate organ etc.)	
<b>Margins</b>	
<b>Positive / Negative</b>	
If positive, indicate site(s) of margin positivity _____	
Margin positive at site of intraprostatic incision _____ Yes/No _____ Site(s)	
Extent of margin involvement (focal vs. non-focal or mm of involvement)*:	
<b>Vascular Invasion</b>	
Present / Absent	
<b>Perineural Invasion</b>	
Present / Absent (optional)	
High grade prostatic intra-epithelial neoplasia: Present / Absent (optional)	
<b>Treatment Effect</b>	
Present / Absent	
<b>Nodal Status</b>	
Lymph nodes submitted: Yes <input type="checkbox"/> No <input type="checkbox"/>	
Right: No. of positive nodes/ No. of nodes submitted AND size of largest lymph node metastasis _____ mm	
Left: No. of positive nodes/ No. of nodes submitted AND size of largest lymph node metastasis _____ mm	
<b>Pathologic stage (AJCC/UICC 7<sup>th</sup> Edition):</b> pT__ N__	

\*Measurement methods should be in accordance with local practice, as there are currently no agreed methodologies.

Synoptic reporting of surgical specimens results in more transparent and complete pathology reporting (Chan et al., 2008). (Mottet et al., 2014)

<b>Recommendation 2.4.6.1</b>	<b>Grade</b>
All radical prostatectomy specimens should be reported with the minimum dataset items as outlined in Table 3.	<b>B</b>

**Clinical question 2.4.7****How do we determine margin status?****Evidence statement**

Current guidelines from the EAU (Mottet et al., 2014) and RCPATH (2009) addressed this question.

The international guidelines are in agreement that margin positivity is an independent prognostic parameter for prostate cancer. Positive surgical margins are defined by microscopic tumour in touch with ink (Mottet et al., 2014, RCPATH, 2009).

A margin status is negative if tumour is very close to the inked surface of the margin (Epstein et al., 2005b) or when they are at the surface of the tissue lacking any ink. (Mottet et al., 2014)

<b>Recommendation 2.4.7.1</b>	<b>Grade</b>
Positive surgical margins are defined by microscopic tumour in touch with ink.	<b>B</b>

<b>Recommendation 2.4.7.2</b>	<b>Grade</b>
A margin status is negative if tumour is very close to the inked surface of the margin or when they are at the surface of the tissue lacking any ink.	<b>B</b>

**Clinical question 2.4.8****Should margin positivity be quantified?****Evidence statement**

A meta-analysis (Stephenson et al., 2009) addressed this question.

Positive surgical margins increase the risk of biochemical recurrence after radical prostatectomy by 2-to 4-fold. The risk of biochemical recurrence may be influenced by the anatomical location and extent of positive surgical margins. In a multicentre study of 7,160 patients treated with radical prostatectomy alone at 1 of 3 institutions between 1995 and 2006, Stephenson et al., (2009) analysed the predictive usefulness of several subclassifications of positive surgical margins.

Positive surgical margins were analysed as solitary vs. multiple, focal vs. extensive and apical location versus other. The usefulness of these subclassifications was assessed by the improvement in predictive accuracy of nomograms containing these parameters compared to one in which the surgical margin was modelled simply as positive vs. negative.

The authors found the 7-year progression-free probability was 60% in patients with positive surgical margins. A positive surgical margin was significantly associated with biochemical recurrence (HR 2.3,  $P < 0.001$ ) after adjusting for age, prostate specific antigen, pathological Gleason score, pathological stage and year of surgery. An increased risk of biochemical recurrence was associated with multiple versus solitary positive surgical margins (adjusted HR 1.4,  $P = 0.002$ ) and extensive versus focal positive surgical margins (adjusted HR 1.3,  $P = 0.004$ ) on multivariable analysis. However, neither parameter improved the predictive accuracy of a nomogram compared to one in which surgical margin status was modelled as positive vs. negative (concordance index 0.851 vs. 0.850 vs. 0.850) (Stephenson et al., 2009).

The authors concluded the number and extent of positive surgical margin significantly influence the risk of biochemical recurrence after radical prostatectomy. However, the empirical prognostic usefulness of sub-classifications of positive surgical margins is limited (Stephenson et al., 2009).

<b>Recommendation 2.4.8.1</b>	<b>Grade</b>
It is optional, according to local practice, to report extent of margin positivity. This can be done either as mm of involvement or by documenting focal versus extensive involvement.	<b>B</b>

**Clinical question 2.4.9**

**For patients undergoing radical prostatectomy, should location of the positive surgical margin be reported?**

**Evidence statement**

A consensus statement from the ISUP (Tan et al., 2011) addressed this question.

While location of positive surgical margin does not predict prostate cancer recurrence, it is recommended internationally that the location of positive surgical margins is reported.

This is one of the tools necessary to audit the quality of surgery and provide feedback to urologists.

The locations of positive margins should be noted as occurring on the left or right and posterior, posterolateral, lateral or anterior at either the apex, mid, or base (or bladder neck) (Tan et al., 2011).

<b>Recommendation 2.4.9.1</b>	<b>Grade</b>
The location of positive margins should be reported. Locations may be noted as follows: left or right and posterior, posterolateral, lateral or anterior at either the apex, mid, or base (or bladder neck).	<b>D</b>

**Clinical question 2.4.10****Should we document, quantify, and specify the location of extraprostatic extension (EPE)?****Evidence statement**

An RCPATH guideline (2009), three cohort studies (Epstein et al., 1993, Marks et al., 2007, Sung et al., 2007) and a retrospective analysis (Wheeler et al., 1998) addressed this question.

EPE is the recommended term for the presence of tumour beyond the confines of the prostate. EPE is defined as carcinoma mixed with periprostatic adipose tissue, or bulging out beyond the contours of the prostate gland (e.g. at the neurovascular bundle or the anterior prostate). Bladder neck invasion is also considered to be an EPE. At the apex of the prostate gland, tumour mixed with skeletal muscle does not constitute EPE.

There is consensus in the literature that EPE should be documented, as extension is related to the risk of recurrence.

There is no agreement in the literature on the optimum method to measure EPE (Fine et al., 2012, RCPATH, 2009). Accepted methods include focal versus extensive (Epstein et al., 1993), <1 high-power field versus >1 high-power field (Wheeler et al., 1998, Marks et al., 2007), and radial measurement in mm (Sung et al., 2007).

Pathologists usually report the location or locations of EPE. This parameter has no known prognostic significance unless there is a positive margin at this site.

<b>Recommendation 2.4.10.1</b>	<b>Grade</b>
Extraprostatic extension should be documented.	<b>B</b>

<b>Recommendation 2.4.10.2</b>	<b>Grade</b>
Extraprostatic extension should be quantified. The method of quantification should be according to local practice.	<b>B</b>

<b>Good practice point</b>
It may be useful to give the location of extraprostatic extension (EPE), as it can be used for audit purposes for clinical, radiology and pathology.

**Clinical question 2.4.11**

**How do we define a dominant tumour nodule in radical prostatectomy specimens?**

**Evidence statement**

There is no consensus as to how a dominant tumour nodule should be defined, e.g. largest nodule vs. nodule with highest Gleason Score (Van Der Kwast, et al., 2011).

**Good practice point**

A dominant tumour nodule, where identifiable, may be defined according to local practice e.g. largest nodule or nodule with the highest Gleason Score.

**Clinical question 2.4.12**

**Is it necessary to give the location of a dominant tumour nodule in radical prostatectomy specimens?**

**Evidence statement**

A review (Fine et al., 2012) addressed this question.

There is some evidence to suggest that anterior located prostatic tumours have a worse prognosis (Al-Ahmadie et al., 2008). If it is possible to identify a dominant tumour nodule in an anterior location then this should be documented (Al-Ahmadie et al., 2008). There is less definitive evidence at this time to specify peripheral vs. transitional location. (Fine et al., 2012)

<b>Recommendation 2.4.12.1</b>	<b>Grade</b>
If it is possible to identify a dominant tumour nodule in an anterior location then this should be documented. There is less definitive evidence at this time to specify peripheral versus transitional location.	<b>D</b>



**Clinical question 2.4.13****Should reporting of pT2 substage (a, b, and c) be optional?****Evidence statement**

An ISUP consensus statement (Van der Kwast et al., 2011) addressed this question.

At the 2009 ISUP consensus the validity of the current pT2 substaging system was discussed after the presentation of background data. The majority (65.5%) of participants felt that the current pT2 substaging of prostate cancers should be discontinued. If the pT2 category was to be maintained, the majority of participants preferred to see a return to a two-tier subcategorisation for pT2 (unilateral versus bilateral prostate cancer) as defined in the 1992 TNM classification. A consensus was achieved for the view that a minimum size or volume measure should be employed as a cutpoint to distinguish unilateral (pT2a) from bilateral (pT2c) cancers, although no agreement was reached as to the defining value of such a cutpoint. It was proposed that for a tumour to be classified as pT2c, the contralateral tumour should be at least 1 cm in diameter (approximately equal to 0.5 ml). It was argued that this would be consistent with the criteria employed for clinical T2 substaging; however, no consensus was reached on this proposal. The conference concluded that consensus was reached to discontinue the use of the current pT2 substaging system. In view of the lack of clinical significance of the current (TNM 2002/2010) pT2 subcategories, there was general agreement in the subsequent discussion for the recommendation that the reporting of pT2 substaging of prostate cancers should be optional. (Van der Kwast et al., 2011)

<b>Recommendation 2.4.13.1</b>	<b>Grade</b>
The reporting of pT2 substage (a, b, and c) is optional as it has not been proven to be of prognostic significance.	<b>B</b>

**Clinical question 2.4.14****For men who have had a radical prostatectomy, should we document prostate cancer volume?****Evidence statement**

Guidelines from the EAU (Mottet et al., 2014) and Oncoline (2007) addressed this question.

The independent prognostic value of the volume of prostate cancer in radical prostatectomy specimens has not been established (Marks et al., 2007, Stamey et al., 2000, Epstein et al., 2005b, Kikuchi et al., 2004, Van Oort et al., 2008). (Mottet et al., 2014)

Calculating tumour volume is labour-intensive and is unlikely to provide additional benefit beyond that of Gleason score, pT-stage, and surgical margin status (Epstein et al., 2004). Reporting tumour dimensions is sufficient. Multiple studies have shown that the maximum tumour diameter correlates well (significantly) with not only tumour volume but also Gleason score, percentage of positive surgical margins, stage, and biochemical recurrence (Renshaw et al., 1998, Eichelberger et al., 2005). (Oncoline, 2007)

It can therefore be recommended that the greatest dimension of the dominant tumour nodule be assessed (if identified), or that a rough estimate of the percentage of cancer tissue in the prostate be provided. (Mottet et al., 2014)

<b>Recommendation 2.4.14.1</b>	<b>Grade</b>
There is insufficient evidence regarding the additional prognostic value of tumour volume to recommend mandatory reporting of prostate cancer volume.	<b>B</b>
<b>Recommendation 2.4.14.2</b>	<b>Grade</b>
It may be recommended to assess the greatest dimension of the dominant tumour nodule, if identified, or to provide a rough estimate of the percentage of cancer tissue in the prostate.	<b>D</b>

## 2.5 Active surveillance

### **Responsibility for the implementation of recommendations**

While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

**Clinical question 2.5.1**

**For men with a histological diagnosis of prostate cancer, what are the inclusion criteria for being offered active surveillance?**

**Evidence statement**

The current EAU guideline (Mottet et al., 2014) and a consensus statement (Montironi et al., 2014) addressed this question.

Choo and co-workers were the first to report on a prospective active surveillance protocol (Choo et al., 2002, Choo et al., 2001). A series with a long follow-up was reported by Klotz et al., (2010). A total of 452 patients with clinical stage T1c or T2a and a PSA of <10µg/L were enrolled. Patients aged 70 years or younger had a Gleason score of <6; patients that were >70 years had a Gleason score of <7 (3+4). Initially, six biopsies were performed, but in recent years the usual extended 12-core protocol was introduced. At a median follow-up of 6.8 years, the 10-year overall survival was 68%. At 10 years, the disease-specific survival was 97.2%, with 62% of men still alive on active surveillance. A total of 30% of patients had, in the end, undergone a radical treatment for the following reasons:

- 48% for a PSA doubling time of <3 years
- 27% for Gleason score progression on repeat biopsies
- 10% because of patient preference. (Mottet et al., 2014)

A variety of additional studies have now been published on active surveillance in clinically organ-confined disease (Dall'Era et al., 2008, Van As et al., 2008, Soloway et al., 2010, Tosoian et al., 2011, Adamy et al., 2011, Bul et al., 2013). Disease-specific survival in low-grade disease in the pre-PSA era was 87% at 10 years with delayed non-curative treatment. However, longer follow-ups are necessary to obtain definitive results. (Mottet et al., 2014)

Active surveillance might mean no treatment at all for patients older than 70 years, while in younger patients it might mean delaying treatment by possibly as long as years. The repeated biopsies that are part of active surveillance might then become important for their potential side-effect on nerve preservation if surgery is subsequently considered. Repeat biopsies may result in an increase in erectile dysfunction observed during active surveillance (Braun et al., 2014). Infectious complications increased after repetitive biopsies with a factor of 1.3 for each set of earlier biopsies in an active surveillance programme (Ehdaie et al., 2014). (Mottet et al., 2014)

Specific inclusion criteria for active surveillance vary across institutions (Dall'Era et al., 2008). Patients are selected for active surveillance on the basis of their age, PSA density (PSA/prostate volume), measures of PSA kinetics, such as PSA velocity, percent of positive biopsy cores, the extent of prostate cancer in any core, and Gleason score 3+3=6 (Dall'Era et al., 2008). Some institutions include patients with intermediate-risk clinical parameters, allowing for inclusion of patients with PSA at diagnosis greater than 10 µg/L or including select men with Gleason score 3+4=7 prostate cancer. (Montironi et al., 2014)

A multicentre clinical trial of active surveillance versus immediate treatment was opened in the USA in 2006. Its results are expected in 2025. (Mottet et al., 2014)

Recommendation 2.5.1.1	Grade
Active surveillance is an option for men with the lowest risk of prostate cancer progression for whom radical treatment is suitable.	C

**Definition for lowest risk for prostate cancer progression:**

cT1c, PSA <10µg/L, biopsy Gleason score ≤6 (at least 12 cores), ≤2 positive cores, minimal biopsy core involvement (<50% cancer per biopsy).

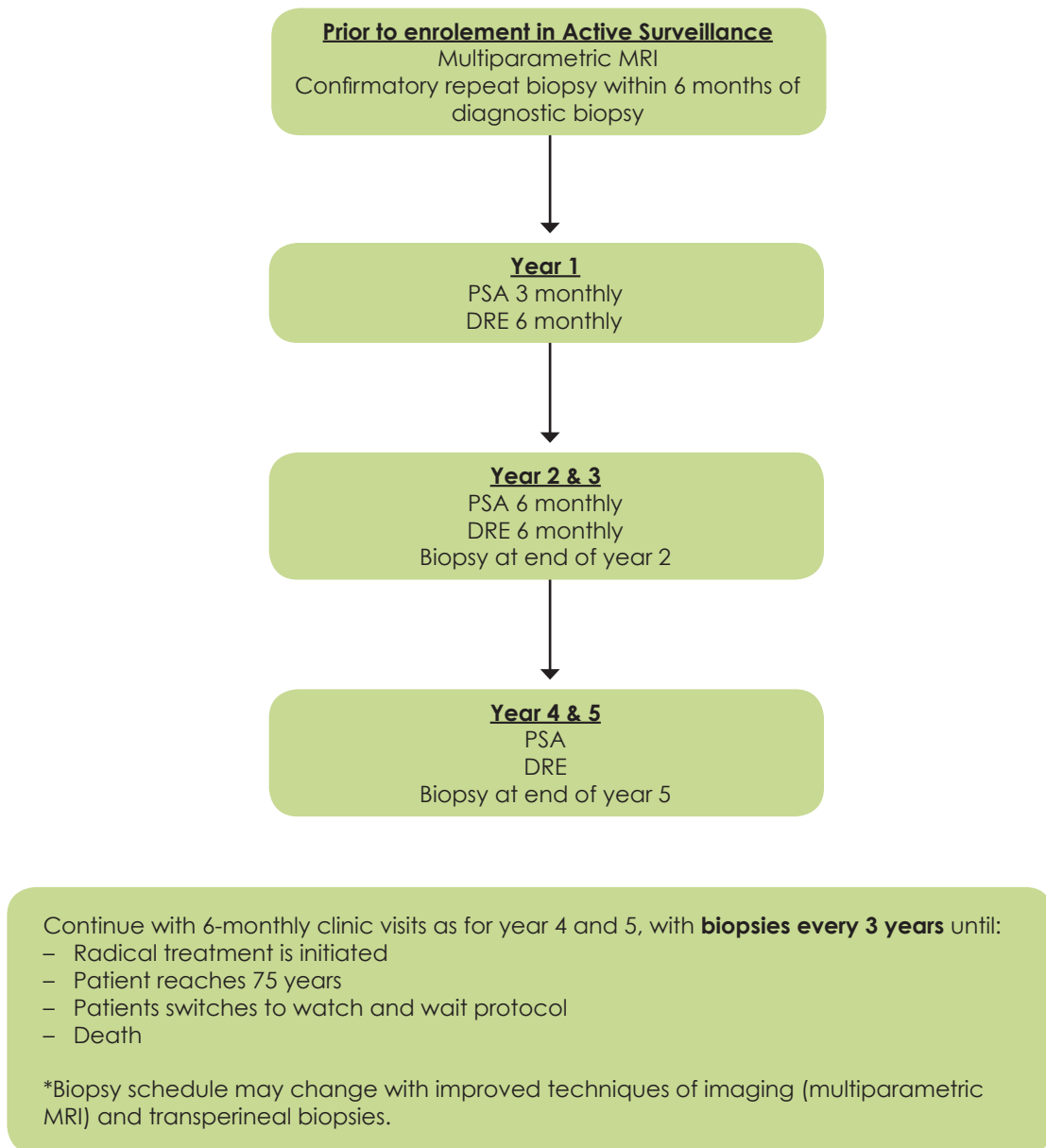
**Clinical question 2.5.2**

**What should active surveillance entail?**

**Evidence statement**

No studies were identified comparing the effectiveness of various active surveillance protocols.

A recent consensus statement (Montironi et al., 2014) concluded that the clinical parameters for patient selection and definition of progression for active surveillance protocols are evolving as data from several large cohorts become mature.



**Figure 1** Protocol for men who have chosen active surveillance

Recommendation 2.5.2.1	Grade
The protocol in Figure 1 is recommended for men who have chosen active surveillance.	<b>D</b>

**Clinical question 2.5.3****Prior to enrolment on active surveillance, should an MRI be performed?****Evidence statement**

The current NICE guideline (2014), a systematic review (Dall'Era et al., 2012) and two cohort studies (Margel et al., 2012, Vargas et al., 2012) addressed this question.

Multiparametric MRI may add additional information and can help to gauge suitability for active surveillance. (NICE, 2014)

Multiple investigators have evaluated MRI for prostate cancer, as this modality offers advantages over other imaging modalities, including enhanced delineation of pelvic anatomy as well as the opportunity for functional assessment. (Dall'Era et al., 2012)

Vargas et al., (2012) assessed adding endorectal MRI to the initial clinical evaluation of 388 men with clinically low-risk prostate cancer. At multivariate analysis patients with higher MRI scores were more likely to have disease upgraded on confirmatory biopsy. The authors concluded that adding endorectal MRI may help predict findings on confirmatory biopsy and assess eligibility for active surveillance.

Margel et al., (2012) investigated the impact of multiparametric endorectal MRI on disease reclassification among 60 active surveillance candidates. The authors concluded that MRI appears to have a high yield for predicting reclassification (18 cases (32.14%)) among men who elect for active surveillance and MRI may be used to better select and guide patients before active surveillance.

<b>Recommendation 2.5.3.1</b>	<b>Grade</b>
Prior to enrolment to an active surveillance programme, a multiparametric MRI scan should be performed.	<b>B</b>

**Clinical question 2.5.4**

**For men being considered for active surveillance what is the maximum number of positive cores, and the greatest percentage of any one core that should allow inclusion in active surveillance?**

**Evidence statement**

A cohort study (Ploussard et al., 2013) and short-term data from the PRIAS study (Bul et al., 2013) addressed this question.

The selection of candidates for active surveillance depends on various factors such as the biopsy and clinical criteria but also the biopsy core number, the prostate volume, and surgeon experience in performing biopsies. Published active surveillance series use different criteria largely based on centre experiences and preferences with no hard data. The most common clinical data used to define active surveillance criteria are a Gleason score  $\leq 6$ , PSA  $\leq 10\mu\text{g/L}$ , and a clinical stage T1c disease. The PSA density and thus indirectly the prostate volume, is noted in inclusion criteria in some studies with different reported cut-offs for active surveillance inclusion. Other characteristics to consider include pathologic biopsy parameters with a wide variation concerning the active surveillance inclusion criteria. Various active surveillance programs include cancers involving  $<3$  cores only and with an extent of cancer in any core  $<50\%$  or involving  $<33\%$  of positive cores. (Ploussard et al. 2013)

Ploussard et al., (2013) used insignificant prostate cancer criteria defined by Epstein et al., (1994) for the selection of active surveillance patients from the Johns Hopkins cohort. Detailed biopsy data at baseline provided additional information on the initial risk of reclassification and significantly predicted initial unfavourable disease in strictly selected active surveillance patients. Patients eligible for active surveillance and having a total tumour length  $<5$  mm and positive cores at midline zone are more likely to have favourable pathologic characteristics at diagnosis. These variables can be used for selection and monitoring improvement in active surveillance programmes. Others variables such as bilaterality, multifocality, or number of positive cores, in this series failed to predict adverse pathologic features in radical prostatectomy specimens in strictly selected low-risk prostate cancer patients.

The PRIAS study found that the strongest predictors for reclassification and switching to deferred treatment were the number of positive cores (two cores compared with one core) and PSA density. The disease-specific survival rate was 100%. Follow-up was too short to draw definitive conclusions about the safety of active surveillance. Limitations of using surrogate end points and markers in active surveillance should be recognised. (Bul et al., 2013)

<b>Recommendation 2.5.4.1</b>	<b>Grade</b>
Given the evidence available from large centre trials, $\leq 2$ positive cores and a maximum of 50% involvement of one core is recommended.	<b>B</b>

### Clinical question 2.5.5

**After initial biopsy, what type of prostate biopsy should be offered to men before being offered active surveillance?**

#### Evidence statement

The current AUA guidelines (2013), two cohort studies (Ayres et al., 2012, Taira et al., 2010), a literature review (Ukimura et al., 2013) and an UpToDate review (Benway and Andriole, 2014) addressed this question.

#### Ultrasound-guided transrectal biopsy (TRUS)

The transrectal ultrasound approach has the ability to guide the physician to obtain specimens in the suspicious areas using a biopsy gun. A template or grid is not used during a TRUS biopsy (AUA, 2013). Twelve cores are taken.

#### Template-guided transperineal biopsy

A template-guided transperineal approach combines transrectal ultrasound with transperineal biopsy, guided by a brachytherapy template (Moran and Braccioforte, 2009, Symons et al., 2013, Kuru et al., 2013). This enhanced localisation augments the biopsy technique and may prove especially beneficial for repeat biopsy when pre-malignant pathology is found on initial biopsy. (Benway and Andriole, 2014)

Prospective randomised trials using extended 12-core schemes revealed no differences between the transrectal and transperineal approach in terms of cancer detection in initial prostate biopsy (Hara et al., 2008, Takenaka et al., 2008). Similarly, in the repeat biopsy setting, both approaches have a similar detection rate in men undergoing saturation biopsy (Abdollah et al., 2011). A retrospective analysis of 1,132 radical prostatectomy specimens revealed that cancers previously detected by transrectal (n = 718) or transperineal (n = 414) prostate biopsy are similar in tumour size (2.0 vs. 1.8 cm<sup>3</sup>, respectively). Furthermore, the rate of insignificant cancer (defined as size <0.5 cm<sup>3</sup>, Gleason ≤6, organ confined) is 5.1% for both (Hossack et al., 2012). Both methods identify the majority of clinically significant cancers (94.9%). Nevertheless, the transperineal approach detected more anterior tumours (16.2%) than the transrectal approach (12%) (Hossack et al., 2012). (Ukimura et al., 2013)

Transperineal template-guided mapping biopsy (TTMB) provides as high a rate of cancer detection as initial biopsy (75.9%) and as repeat biopsy (46.9%). Over half of all cancers found were Gleason ≥7; and only a small minority of cancers were potentially insignificant (11.1%). The distribution of cancers identified in men with multiple prior transrectal biopsies suggests that a template-guided transperineal approach allows better access to the anterior and apical aspects of the gland, in which clinically significant prostate cancer is often located. Increased ability to diagnose apical and anterior disease has implications for men undergoing active surveillance, those who are considering subtotal prostate gland treatment, those with initial negative biopsy but persistently elevated PSA, and those considering minimally invasive treatment options. (Taira et al., 2010)

Ayres et al., (2012) found 34% of men had more significant prostate cancer on restaging transperineal template biopsies compared with their transrectal biopsies. Of these men, 44% had disease predominantly in the anterior part of the gland, an area often under-sampled by transrectal biopsies. In the group of men who had their restaging transperineal template biopsies within six months of commencing active surveillance 38% had more significant disease. There was no correlation with PSA velocity or PSA doubling time. In total, 33% of men stopped active surveillance and had radical treatment. Around one-third of men had more significant prostate cancer on transperineal template biopsies. This probably reflects under-sampling by initial transrectal biopsies rather than disease progression.



<b>Recommendation 2.5.5.1</b>	<b>Grade</b>
A repeat prostate biopsy is mandatory for all patients considering active surveillance and this can be done by either the transrectal or transperineal approach.	<b>B</b>

<b>Recommendation 2.5.5.2</b>	<b>Grade</b>
There is emerging evidence that transperineal biopsies identify more clinically important prostate cancer.	<b>C</b>

**Clinical question 2.5.6**

**For men undergoing active surveillance what are the triggers for conversion to radical treatment?**

**Evidence statement**

The current NICE guidelines (2014) addressed this question.

No trigger factors for conversion to active treatment have been validated. There is broad agreement around a rapidly rising PSA, Gleason score progression, increased tumour volume (core number and/or core percentage involvement), DRE changes and patient preference.

Four analyses (Selvadurai et al., 2013, Klotz et al., 2010, Khatami et al., 2009, Khatami et al., 2007) from three studies were found which reported on the effectiveness of relevant prognostic factors to predict biochemical progression or conversion-free survival. (NICE, 2014)

**Predictive Prognostic Factors**

- PSA velocity (Selvadurai et al., 2013)
- PSA level at diagnosis (Klotz et al., 2010, Khatami et al., 2009)

**Non Predictive Prognostic Factors**

- PSA density (Selvadurai et al., 2013)
- Free-to-total PSA (Selvadurai et al., 2013, Khatami et al., 2007)
- Total cancer length at biopsy (Khatami et al., 2007)
- Tumour volume (Khatami et al., 2009)

**Equivocal Prognostic Factors**

- PSA doubling time (Klotz et al., 2010, Khatami et al., 2009, Khatami et al., 2007)
- Gleason score at diagnosis (Selvadurai et al., 2013, Klotz et al., 2010, Khatami et al., 2009)
- Clinical stage at diagnosis (Selvadurai et al., 2013)

Recommendation 2.5.6.1	Grade
Criteria for conversion to active treatment include: <ul style="list-style-type: none"> <li>- Change in PSA</li> <li>- Change in DRE findings</li> <li>- Upgrade of disease (including increase in core volume, increase in number of positive cores and increase in Gleason grade)</li> <li>- MRI findings suggestive of disease progression</li> <li>- Patient preference for radical treatment</li> </ul>	<b>D</b>

## 2.6 Surgery

### **Responsibility for the implementation of recommendations**

While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

**Clinical question 2.6.1****Is radical prostatectomy a treatment option for men with low-risk prostate cancer (cT1-T2a and Gleason score  $\leq 6$  and PSA less than 10 $\mu$ g/L)?****Evidence statement**

Guidelines from the EAU (Mottet et al., 2014) and Oncoline (2007) addressed this question.

Radical prostatectomy is a treatment option for men with low-risk prostate cancer (Mottet et al., 2014).

Based on the available evidence on the treatment of patients with localised prostate cancer, no recommendations can be made regarding which treatment is preferred. Based on the reported adverse events and complications, a specific treatment cannot be recommended. (Oncoline, 2007)

The choice of treatment is determined after consultation with the patient whom the clinician should inform thoroughly and as objectively as possible regarding the efficacy and toxicity of each treatment modality. The patient's age and general condition are taken into account in the decision, particularly when considering the option of withholding treatment.

There is a potential for overtreatment.

<b>Recommendation 2.6.1.1</b>	<b>Grade</b>
Radical treatment may be an option for men with low-risk prostate cancer and life expectancy of $\geq 10$ years.	<b>C</b>
<b>Recommendation 2.6.1.2</b>	<b>Grade</b>
If radical treatment is being provided, then radical prostatectomy is a treatment option for men with low-risk prostate cancer.	<b>B</b>

**Clinical question 2.6.2****Is radical prostatectomy a treatment option for patients with intermediate-risk prostate cancer and a life expectancy of greater than 10 years?****Evidence statement**

Guidelines from the EAU (Mottet et al., 2014) and Oncoline (2007) and an RCT (Bill-Axelson et al., 2014) addressed this question.

Radical prostatectomy is a treatment option for men with intermediate-risk prostate cancer with a life expectancy of >10 years (Mottet et al., 2014).

Bill-Axelson et al., (2014) report that the number needed to treat (NNT) to avert one death was 8 overall and 4 for men younger than 65 years of age.

Results are dependent on T stage, initial PSA (iPSA), Gleason score, and the level of surgical experience. It should be noted that the results from large studies were all derived from patients treated in the era prior to PSA assessment, Gleason classification, and adequate staging using advanced imaging techniques. (Oncoline, 2007)

There is evidence that the rate of complications following radical prostatectomy is lower when the operation is performed in a high-volume hospital and by an urologist who has performed this procedure regularly (Ellison et al., 2000, Hu et al., 2006, Begg et al., 2002). (Oncoline, 2007)

However, no relationship has been demonstrated between cancer specific survival and the number of procedures performed (open or laparoscopic). (Oncoline, 2007)

<b>Recommendation 2.6.2.1</b>	<b>Grade</b>
Radical treatment is recommended for men with intermediate-risk prostate cancer with a life expectancy of ≥10 years.	<b>B</b>

<b>Recommendation 2.6.2.2</b>	<b>Grade</b>
Radical prostatectomy is a treatment option for men with intermediate-risk prostate cancer with a life expectancy of ≥10 years.	<b>B</b>

<b>Good practice point</b>
All surgery should be performed in high-volume hospitals to reduce complications.

**Clinical question 2.6.3****Is radical prostatectomy a treatment option for patients with high-risk localised and locally advanced prostate cancer?****Evidence statement**

The current EAU guideline (Mottet et al., 2014) addressed this question.

Patients classified with high-risk prostate cancer are at an increased risk of PSA failure, the need for secondary therapy, metastatic progression and death from prostate cancer. Nevertheless, not all high-risk prostate cancer patients have a uniformly poor prognosis after radical prostatectomy (Yossepowitch et al., 2007). (Mottet et al., 2014)

There is no consensus regarding the optimal treatment of men with high-risk prostate cancer. Decisions on whether to elect surgery as local therapy should be based on the best available clinical evidence. Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, radical prostatectomy is a reasonable first step in selected patients with a low tumour volume. Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances. (Mottet et al., 2014)

Surgery can be carried out with curative intent or to achieve local control. The potential side effects of surgery must be weighed against the potential benefits.

Radical prostatectomy will be curative in a select group of high-risk patients with prostate cancer. It should be considered either singularly or as a component of combined therapy.

Although still controversial, it is increasingly evident that surgery has a place in treating locally advanced disease (Gerber et al., 1997, Ward et al., 2005, Hsu et al., 2007). (Mottet et al., 2014)

Recommendation 2.6.3.1	Grade
Radical prostatectomy may be considered as a treatment option in high-risk disease, either alone or in combination with other therapies.	C

**Clinical question 2.6.4**

**During a radical prostatectomy, is an extended lymph node dissection (lymphadenectomy) indicated over a standard (limited) lymph node dissection in all patients?**

**Evidence statement**

The current EAU guideline (Mottet et al., 2014) addressed this question.

Extended lymph node dissection (eLND) includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. (Mottet et al., 2014)

If a lymph node dissection is being performed then an extended lymph node dissection is recommended. A limited lymph node dissection (LND) is not recommended. (Mottet et al., 2014)

Patients with PSA <10µg/L and biopsy Gleason score <7 have a low-risk of lymph node metastasis and therefore eLND might not be beneficial. (Mottet et al., 2014)

If the risk for lymph node metastases exceeds 5%, according to the EAU nomogram, then an extended lymph node dissection is necessary.

<b>Recommendation 2.6.4.1</b>	<b>Grade</b>
A lymph node dissection is not necessary in low-risk, localised prostate cancer, because the risk for positive lymph nodes does <b>not</b> exceed 5%.	<b>B</b>

<b>Recommendation 2.6.4.2</b>	<b>Grade</b>
Extended lymph node dissection should be performed in intermediate-risk, localised prostate cancer if the estimated risk for positive lymph nodes exceeds 5%, using an available nomogram.	<b>B</b>

<b>Recommendation 2.6.4.3</b>	<b>Grade</b>
Extended lymph node dissection should be performed in high-risk cases. In these circumstances, the estimated risk for positive lymph nodes is 15%-40%.	<b>B</b>

<b>Good practice point</b>
Limited lymph node dissection should no longer be performed, because it misses at least half of the nodes involved.

## 2.7 Medical oncology

### **Responsibility for the implementation of recommendations**

While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.



**Clinical question 2.7.1**

**In men with prostate cancer who have biochemical/clinical relapse following definitive treatment, when should you commence hormonal therapy?**

**Evidence statement**

Guidelines from the NCCN (2014) and Oncoline (2007) addressed this question.

The question whether hormone therapy should be started immediately after a diagnosis of metastatic prostate cancer or delayed until subjective, biochemical, or objective progression occurs has been a point of discussion for years (Newling, 2001). The number of studies addressing this topic is limited, and the available studies have reported conflicting results and have methodological flaws (Nesbit and Baum, 1950, Byar and Corle, 1988). (Oncoline, 2007)

The timing of androgen deprivation therapy (ADT) for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient anxiety, and the short and long-term effects of ADT. (NCCN, 2014)

Most patients will have a good 15 year prognosis. Their prognosis is however best approximated by the absolute level of PSA, the rate of change in the PSA level (PSADT), and the initial stage, grade, and PSA level at the time of definitive therapy. (NCCN, 2014)

Earlier ADT may be better than delayed ADT, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early ADT is not clear, treatment should be individualised until definitive studies are done. Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier. (NCCN, 2014)

<b>Recommendation 2.7.1.1</b>	<b>Grade</b>
The evidence that favours immediate hormone therapy over delayed therapy is not convincing. Therefore, this choice should be made on an individual basis for each patient. Relevant factors include patient preference, the presence of symptoms (i.e. pain), the extent of metastases, PSADT, age, comorbidity, and the effect of treatment on quality of life.	<b>C</b>

### Clinical question 2.7.2

## Is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer?

### Evidence statement

The current NICE guideline (2014) addressed this question.

### Overall survival

Moderate quality evidence from six randomised trials shows no significant difference in overall survival between men treated with intermittent hormone therapy and those treated with continuous hormone therapy ( $P=0.17$ ; only five included in meta-analysis). However, the most recent randomised study (Hussain et al., 2013) suggested an inferior overall survival outcome for the intermittent ADT approach (5.8 vs. 5.1 years). (NICE, 2014)

### Progression-free survival (not biochemical)

Low quality evidence from two randomised trials found no significant difference in progression-free survival between intermittent and continuous therapy. However, both trials included both clinical and biochemical progression in their definition of disease progression. Three studies also provided very low quality evidence of no significant difference in progression-free survival between intermittent and continuous treatment groups for clinical progression. (NICE, 2014)

### Adverse events

One moderate quality study found the incidence of treatment-emergent adverse events to be borderline significantly higher in the continuous treatment group ( $P = 0.042$ ) (Mottet et al., 2009, Mottet et al., 2012). However, two further studies provided low quality evidence of no significant difference in the rates of adverse events between groups but provided no figures. Crook et al., (2012, 2011) and Duncan et al., (2011) also reported no significant difference between treatment arms in the rate of cardiovascular events or osteoporotic fractures (but did not provide figures). Hering et al., (2000) observed fewer mild adverse events (gastrointestinal, gynaecomastia and fatigue) and severe adverse events (severe nausea/vomiting and oedema of the lower limb) with intermittent than with continuous therapy (relative risk (RR) 0.29 and 0.15, respectively). (NICE, 2014)

Low quality evidence from two randomised trials suggests that hot flushes are significantly less likely with intermittent than with continuous hormone therapy. While both studies reported fewer hot flushes with intermittent therapy (RR 0.66 and 0.97, respectively) there is uncertainty about the size of the effect due to heterogeneity. (NICE, 2014)

Moderate quality evidence from one randomised trial (Calais da Silva et al., 2011, 2009, 2003) shows gynaecomastia is less likely in men treated with intermittent than with continuous hormone therapy (RR 0.64, 95% CI 0.43-0.93). The evidence suggests that for every 100 men treated with intermittent instead of continuous therapy, there would be seven fewer cases of gynaecomastia. Crook et al., (2012, 2011) and Duncan et al., (2011) also reported patients receiving intermittent therapy had significantly less gynaecomastia than those receiving continuous therapy but no effect size was reported ( $P<0.001$ ). (NICE, 2014)

Low quality evidence from one randomised trial (Calais da Silva et al., 2011, 2009, 2003) suggests sexual activity within the previous month was more likely during intermittent therapy than during continuous therapy (RR 2.90, 95% CI 1.52-5.53). The evidence suggests for every 100 men treated with intermittent instead of continuous therapy there would be an additional 18 reporting sexual activity within the previous month. Low quality evidence from another randomised trial (Hering et al., 2000) found impotence was much less likely in men receiving intermittent than in those on continuous therapy (RR 0.06, 95% CI 0.01-0.28). While Crook et al., (2012, 2011) and Duncan et al., (2011) reported that patients receiving intermittent therapy had significantly greater desire

for sexual activity and better erectile function than those receiving continuous therapy but no effect sizes were reported ( $P<0.001$ ). Miller et al., (2007) also found self-assessed sexual activity to be better with intermittent therapy but no effect sizes were reported. (NICE, 2014)

### **Health-related quality of life**

Very low quality evidence from five randomised trials suggests better quality of life with intermittent than with continuous therapy. The studies reported that patients receiving intermittent therapy had significantly better physical function ( $P<0.001$ ), overall self-assessed health ( $P<0.001$ ), and physical and emotional scores, but did not report the actual figures. (NICE, 2014)

However, one moderate quality study did not find any significant difference between the treatment groups using the QLQ-C30 but did not provide figures (Mottet et al., 2009). Another study found that those in the intermittent group were significantly less likely to report impotence ( $P<0.001$ ) or poor mental health ( $P=0.003$ ) at 3 months (Hussain et al., 2013). At 9 months patients in the intermittent group were more likely to report high libido ( $P=0.01$ ) and less likely to report impotence ( $P<0.001$ ). However, at 15 months there remained no significant difference between groups in any of the quality of life outcomes. Salonen et al., (2013) found significant differences in sexual functioning but not activity limitation or physical capacity, favouring intermittent treatment at a median follow-up of 65 months, but did not report individual scores or outcomes of other domains. (NICE, 2014)

Evidence on treatment-related morbidity and mortality and patient acceptability was not reported by any of the included studies.

<b>Recommendation 2.7.2.1</b>	<b>Grade</b>
For patients with biochemical relapse or metastatic recurrence continuous androgen deprivation therapy is the standard option.	<b>B</b>
<b>Recommendation 2.7.2.2</b>	<b>Grade</b>
Intermittent androgen deprivation therapy can be considered an acceptable alternative option to be discussed with patients.	<b>B</b>

**Clinical question 2.7.3****Should androgen deprivation therapy be continued in patients who develop castration resistant prostate cancer?****Evidence statement**

The current EAU guideline (Mottet et al., 2014) addressed this question.

Eventually men with prostate cancer show evidence of disease progression despite castration. In this situation continued testicular androgen suppression in castration resistant prostate cancer (CRPC) is debatable, as suggested by Mani et al., (1988). (Mottet et al., 2014)

These data have been challenged by two trials that showed only a marginal survival benefit for patients remaining on luteinising hormone-releasing hormone (LHRH) analogues during second- and third-line therapies (Taylor et al., 1993, Hussain et al., 1994). However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. In addition nearly all subsequent treatments have been studied in men with ongoing androgen suppression and therefore it should be continued indefinitely in these patients. (Mottet et al., 2014)

Recommendation 2.7.3.1	Grade
Androgen deprivation therapy should be continued indefinitely in these patients.	D

**Good practice point**

When men with prostate cancer develop biochemical evidence of castration resistant prostate cancer, their treatment options should be discussed by the urological cancer multidisciplinary team with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate.

### **Clinical question 2.7.4**

#### **Is secondary hormone therapy beneficial in patients with castration resistant prostate cancer?**

##### **Evidence statement**

The current NCCN (2014) guideline and four RCTs (Beer et al., 2014, Logothetis et al., 2012, Ryan et al., 2013, Scher et al., 2012) addressed this question.

In the setting in which patients are docetaxel naïve and have no or minimal symptoms, administration of secondary hormonal manipulations including the addition of, or switching to, a different antiandrogen (flutamide, bicalutamide, nilutamide, enzalutamide), addition of adrenal/paracrine androgen synthesis inhibitors (ketoconazole or abiraterone (+ prednisone)), or use of an oestrogen, such as diethylstilbestrol (DES), can be considered. (NCCN, 2014)

Ryan et al., (2013) found that abiraterone improved radiographic progression-free survival (16.5 months with abiraterone-prednisone and 8.3 months with prednisone alone; hazard ratio for abiraterone-prednisone vs. prednisone alone, 0.53; 95% confidence interval [CI], 0.45 to 0.62;  $P<0.001$ ), showed a trend toward improved overall survival (25% decrease in the risk of death in the abiraterone-prednisone group, median not reached, vs. 27.2 months for prednisone alone; hazard ratio, 0.75; 95% CI, 0.61 to 0.93;  $P=0.01$ ), and significantly delayed clinical decline (time to decline, 12.3 vs. 10.9 months; hazard ratio for decline, 0.82; 95% CI, 0.71 to 0.94;  $P=0.005$ ) and initiation of chemotherapy in patients with metastatic CRPC (mCRPC) (median time to the initiation of cytotoxic chemotherapy was 25.2 months in the abiraterone-prednisone group vs. 16.8 months in the prednisone-alone group; hazard ratio, 0.58; 95% CI, 0.49 to 0.69;  $P<0.001$ ).

In a double-blind, phase 3 study, Beer et al. (2014) randomly assigned 1717 patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily. The co-primary end points were radiographic progression-free survival and overall survival.

The study was stopped after a planned interim analysis showed a benefit of the active treatment. The rate of radiographic progression-free survival at 12 months was 65% among patients treated with enzalutamide, as compared with 14% among patients receiving placebo (81% risk reduction; hazard ratio in the enzalutamide group, 0.19; 95% CI, 0.15 to 0.23;  $P<0.001$ ). A total of 626 patients (72%) in the enzalutamide group, as compared with 532 patients (63%) in the placebo group, were alive at the data-cutoff date (29% reduction in the risk of death; hazard ratio, 0.71; 95% CI, 0.60 to 0.84;  $P<0.001$ ). The benefit of enzalutamide was shown with respect to all secondary end points, including time to initiation of cytotoxic chemotherapy (hazard ratio, 0.35), time to first skeletal-related event (hazard ratio, 0.72), a complete or partial soft-tissue response (59% vs. 5%), time to PSA progression (hazard ratio, 0.17), and a rate of decline of at least 50% in PSA (78% vs. 3%) ( $P<0.001$  for all comparisons). Fatigue and hypertension were the most common clinically relevant adverse events associated with enzalutamide treatment. These results showed enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer.

Scher et al. (2012) concluded that enzalutamide significantly prolonged the survival of men with mCRPC after chemotherapy (18.4 months (95% confidence interval [CI], 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (hazard ratio for death in the enzalutamide group, 0.63; 95% CI, 0.53 to 0.75;  $P<0.001$ ).

In patients with mCRPC previously treated with docetaxel, Logothetis et al. (2012) found abiraterone (+ prednisone) offer significant benefits compared with prednisone alone in terms of pain relief (157 of 349 [45%] patients vs. 47 of 163 [29%] respectively;  $P=0.0005$ ), delayed pain progression, and prevention of skeletal-related events (time to first skeletal related event: 25.0 months [95% CI 25.0-not estimable] vs. 20.3 months [16.9-not estimable] respectively;  $P=0.0001$ ).

Recommendation 2.7.4.1	Grade	Resource Implications
For men with castration resistant prostate cancer, second line hormone therapy should be considered.	A	–

Recommendation 2.7.4.2	Grade	Resource Implications
For men with castration resistant prostate cancer in whom chemotherapy is <b>not</b> yet clinically indicated, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide.	A	Enzalutamide is licensed for this indication in the ROI and is currently being reviewed by the HSE under the pricing and reimbursement framework agreed by the DOH with the pharmaceutical industry.

Recommendation 2.7.4.3	Grade	Resource Implications
For men with castration resistant prostate cancer, whose disease has progressed on or after a docetaxel-based chemotherapy regimen, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide.	A	–

**Clinical question 2.7.5**

**Which treatment options are beneficial for patients with castration resistant prostate cancer?**

**Evidence statement**

Six high quality phase III RCTs on the treatment for CRPC, with many therapeutic options in this setting (Beer et al., 2014, De Bono et al., 2011, Logothetis et al., 2012, Parker et al., 2013, Ryan et al., 2013, Scher et al., 2012) addressed this question.

Where there is no evidence of metastases, second-line hormonal options would be preferred to chemotherapy.

Where there is evidence of metastases (mCRPC):

- In patients with no symptoms, second-line hormonal options may be preferred to chemotherapy.
- In patients with symptoms, chemotherapy may be prioritised in order to produce a rapid response. It is recognised that certain patients may not be suitable for chemotherapy. The optimal sequencing of the newer agents is yet to be determined.

Third or further lines of treatment may be considered in patients who have maintained performance status. Choice would depend on previous treatment.

A phase III, randomised, double-blind, placebo-controlled study for the treatment of adults with castration resistant prostate cancer, symptomatic bone metastases and no known visceral metastases (Parker et al., 2013), which was terminated for efficacy at the pre-specified interim analysis concluded that radium-223 improved overall survival (median, 14.9 months versus 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83;  $P < 0.001$ ).

Recommendation 2.7.5.1	Grade	Resource Implications
Clinicians should offer treatment with abiraterone (+ prednisone), cabazitaxel or enzalutamide to patients with metastatic castration resistant prostate cancer with good performance status who have received prior docetaxel chemotherapy.	A	–

Recommendation 2.7.5.2	Grade	Resource Implications
Abiraterone (+ prednisone) or enzalutamide may also be considered in patients who have <b>not</b> received docetaxel.	A	Enzalutamide is licensed for this indication in the ROI and is currently being reviewed by the HSE under the pricing and reimbursement framework agreed by the DOH and the HSE with the pharmaceutical industry.

Recommendation 2.7.5.3	Grade	Resource Implications
Patients with metastatic castration resistant prostate cancer who have predominantly bone metastases may benefit from radium-223.	A	–

### Clinical question 2.7.6

## Is treatment with bisphosphonates beneficial in patients with castration resistant prostate cancer?

### Evidence statement

A recent UpToDate review (Sartor and DiBiase, 2014) addressed this question.

The benefit of zoledronic acid in men with bone metastases and CRPC was demonstrated in a trial in 643 men whose disease was progressing while on ADT (Saad et al., 2002). Men were randomly assigned to one of two doses of zoledronic acid (4mg or 8mg) or placebo, each given every three weeks. The 8 mg dose of zoledronic acid was reduced to 4mg early in the trial because of an increased risk of renal toxicity. At an average follow-up of 24 months, there was a significant reduction in the frequency of skeletal related events in men receiving zoledronic acid compared to placebo (38% vs. 49%), and the median time to develop a skeletal related events was significantly longer with zoledronic acid (488 days vs. 321 days) (Saad et al., 2004). Pain and analgesic scores were significantly higher in men who received the placebo than in those who received zoledronic acid, but there were no differences in disease progression, performance status, or quality-of-life scores among the groups. (Sartor and DiBiase, 2014)

In a double-blind phase III trial 1901 men with CRPC and at least one bone metastases were randomly assigned to denosumab (120mg) or zoledronic acid (4mg), each given every four weeks (Fizazi et al., 2011). Patients on both treatment arms were advised to use calcium and vitamin D supplements. The primary objective of the study was time to first skeletal-related event (pathologic fracture, need for radiation therapy or surgery, or spinal cord compression). (Sartor and DiBiase, 2014)

At a median follow-up of approximately 12 months, results included the following:

- The time to first skeletal-related event was significantly delayed with denosumab compared to zoledronic acid (median 20.7 vs. 17.1 months, HR 0.82, 95% CI 0.71-0.95).
- There was no statistically significant difference in either overall survival (19.4 vs. 19.8 months, HR 1.03) or time to disease progression (8.4 months with both regimens, HR 1.06).
- Both treatments were well tolerated. Osteonecrosis of the jaw tended toward being more frequent with denosumab compared with zoledronic acid (2.3% vs. 1.3%) although these differences were not statistically significant. Hypocalcaemia was also significantly more frequent with denosumab (13% vs. 6%). (Sartor and DiBiase, 2014)

The main side effects of denosumab are fatigue, nausea and hypophosphataemia (BCCA, 2012). Post marketing experience suggests a small risk of significant hypocalcaemia especially in vulnerable patients (e.g. elderly, frail, renal impairment, at risk of non compliance with calcium supplements).

The toxicity of bisphosphonates and denosumab includes osteonecrosis of the jaw and electrolyte disturbance. Bisphosphonates can also cause nephrotoxicity. Serum creatinine and electrolytes including calcium should be obtained prior to each dose with appropriate dose modification or omission if results are abnormal.



<b>Recommendation 2.7.6.1</b>	<b>Grade</b>	<b>Resource Implications</b>
<p>For men with castration resistant prostate cancer and bone metastases, treatment with zoledronic acid should be considered. Consider denosumab for men in whom zoledronic acid is contraindicated or not tolerated.</p>	<p><b>A</b></p>	<p>In 2011, the NCPE considered denosumab a cost-effective therapy for the prevention of skeletal-related events in adults with bone metastases from solid tumours as compared with zoledronic acid. The cost of zoledronic acid has changed considerably in the interim. The market price of zoledronic acid is estimated to be below €50. The HSE high tech reimbursed price of denosumab (Xgeva®) is €356.99. In the absence of a formal re-appraisal of the cost effectiveness of denosumab the drug acquisition cost changes would suggest that zoledronic acid is likely to be the most cost effective treatment option in this patient cohort.</p>

## 2.8 Radiation oncology

### **Responsibility for the implementation of recommendations**

While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

### **Clinical question 2.8.1**

#### **Which subgroup of patients will benefit from adjuvant radiotherapy after radical prostatectomy?**

##### **Evidence statement**

The current EAU guideline (Mottet et al., 2014) and a cohort study (Stephenson et al., 2007) addressed this question.

Three prospective randomised trials have assessed the role of immediate postoperative radiotherapy (RT) (Bolla et al., 2012, Swanson et al., 2008, Wiegel et al., 2009a). (Mottet et al., 2014)

They were well conducted clinical trials. There were methodological differences in the Wiegel et al., (2009a) trial, in that patients had undetectable PSA at point of randomisation.

The updated results of the SWOG 8794 trial, with a median follow-up of more than 12 years, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved metastasis-free survival, with a ten year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years,  $P=0.016$ ) and a ten year overall survival of 74% vs. 66% (median: 1.9 years prolongation;  $P=0.023$ ) (Swanson et al., 2008). (Mottet et al., 2014)

EORTC 22911 (Bolla et al., 2012), with a target sample size of 1005 patients, compared immediate postoperative radiotherapy (60 Gy) with radiotherapy delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 with risk factors R1 and pT2R1 after retropubic radical prostatectomy. Immediate postoperative radiotherapy was well tolerated. Grade 4 toxicity was not observed. The rate of grade 3 genitourinary toxicity was 5.3% versus 2.5% in the observation group after 10 years. For patients younger than 70, the study concluded that immediate postoperative radiotherapy after surgery significantly improved the 10-year biological progression free survival (PFS): 60.6% vs. 41.1%. A difference observed in the clinical progression rates for the entire cohort that favoured adjuvant RT after 5 years was not sustained after 10 years, although locoregional control was better in the long-term follow-up after immediate irradiation (hazard ratio, HR = 0.45,  $P < 0.0001$ ). However, adjuvant RT patients with pT2-3 R1 also showed an improved clinical PFS after 10 years (HR = 0.69;  $P = 0.008$ ). Overall survival did not differ significantly between the treatment arms. After re-evaluation using a central pathological review, the highest impact of adjuvant RT was found to be on the biochemical progression (HR down to 0.3) seen in patients with positive margins, but there was also a positive effect of 10% after 5 years for pT3 with negative margins and other risk factors (Van der Kwast et al., 2007, Wiegel et al., 2009a). (Mottet et al., 2014)

It should be noted that the rate of salvage radiotherapy (SRT) was much greater in the EORTC study than the SWOG study, potentially diluting the benefit of adjuvant radiotherapy (ART) in the EORTC study. In the EORTC 47.5% (95% CI 42.7%-52.4%) of the wait-and-see group receiving salvage treatment with 30.8% of the wait-and-see group receiving radiotherapy as the first salvage treatment.

### Detectable PSA postoperatively

Men with detectable PSA postoperatively should be considered for postoperative radiotherapy in the adjuvant setting (Stephenson et al., 2007, Siegmann et al., 2012).

Early SRT provides possibility of cure for patients with an increasing or persistent PSA after radical prostatectomy. More than 60% of patients who are treated before the PSA level rises to >0.5 µg/L will achieve an undetectable PSA level again (Stephenson et al., 2007, Pfister et al., 2014, Siegmann et al., 2012, Ohri et al., 2012), providing patients with an ~80% chance of being progression-free 5 years later (Wiegel et al., 2009b). A retrospective analysis based on 635 patients who underwent radical prostatectomy in 1982-2004, followed up through December 2007, who experienced biochemical and/or local recurrence and received no salvage treatment (n = 397) or SRT alone (n = 160) within 2 years of biochemical recurrence, showed that SRT was associated with a threefold increase in the prostate cancer-specific survival relative to those who received no salvage treatment ( $P < 0.001$ ). SRT has also been effective in patients with a rapid PSADT (Trock et al., 2008). Despite the indication of SRT also a “wait and see”-strategy is an option in patients with a long PSADT of more than 12 months (Boorjian et al., 2011). (Mottet et al., 2014)

The addition of hormone therapy to SRT (n = 78) was not associated with any additional increase in the cancer specific survival; compared with SRT alone (Trock et al., 2008). So far, adding ADT to SRT has shown only some benefit in terms of biochemical progression free survival after 5 years in retrospective series (Goenka et al., 2012, Choo et al., 2009) and for PFS for “high-risk”-tumours (Soto et al., 2012), but data from prospective randomised trials are missing. Results are awaited from a recently completed randomised controlled phase III study from the Radiation Therapy Oncology Group (RTOG-9061) comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the postoperative setting. To date there is no recommendation for patients with primary pN0-stage at radical prostatectomy for a combination of SRT plus additional ADT. (Mottet et al., 2014)

Both approaches (ART and SRT) together with the efficacy of neoadjuvant hormone therapy are currently being compared in three prospectively randomised clinical trials: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) in the United Kingdom, the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES), and Groupe d'Etude des Tumeurs Uro-Génitales (GETUG). (Mottet et al., 2014)

Decision making on whether to proceed with adjuvant RT for high-risk prostate cancer (pT3-4 pN0 M0 with undetectable PSA) after radical prostatectomy, or to postpone RT as an early salvage procedure in case of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before radical prostatectomy that adjuvant radiotherapy may be administered if the patient has negative prognostic risk factors. Ultimately, the decision on whether to treat requires a multidisciplinary approach that takes into account the optimal timing of radiotherapy when it is used and provides justification when it is not, and this will help the discussion between the physician and the patient. (Mottet et al., 2014)

While awaiting the results of ongoing randomised controlled trials, salvage radiotherapy is recommended for patients who develop a detectable PSA, in the absence of metastatic disease (Stephenson et al., 2007).

Recommendation 2.8.1.1	Grade
<b>Undetectable PSA postoperatively</b> Patients who are classified as margin positive or with seminal vesicle involvement after radical prostatectomy, should be considered for adjuvant radiotherapy.	<b>A</b>

<b>Recommendation 2.8.1.2</b>	<b>Grade</b>
<b>Undetectable PSA postoperatively</b> Patients who are classified as margin negative and who have no other adverse prognostic features should be monitored, pending the results of ongoing clinical trials (e.g. RADICALS, RAVES, GETUG), with early salvage radiotherapy when PSA becomes detectable using ultrasensitive PSA assay.	<b>A</b>

<b>Recommendation 2.8.1.3</b>	<b>Grade</b>
<b>Detectable PSA postoperatively</b> Salvage radiotherapy is recommended for patients who develop a detectable PSA, in the absence of metastatic disease.	<b>B</b>

<b>Good practice point</b> Patients with detectable PSA postoperatively should be considered for postoperative radiotherapy in the adjuvant setting.
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**Clinical question 2.8.2**

**Is external beam radiation therapy (EBRT) and/or brachytherapy a treatment option for the following categories of prostate cancer:**

- **Low-risk prostate cancer**
- **Intermediate-risk prostate cancer**
- **High-risk prostate cancer**
- **Very-high-risk prostate cancer**

**Evidence statement**

Twelve RCTs (Armstrong et al., 2011, Bolla et al., 2002, Crook et al., 2004, D'Amico et al., 2011, Dearnaley et al., 2007, Denham et al., 2011, Jones et al., 2011, Lawton et al., 2005, Pilepich et al., 2001, Pisansky et al., 2013, Warde et al., 2011, Widmark et al., 2009), five cohort studies (Alicikus et al., 2011, D'Amico et al., 2004, Eade et al., 2007, Kuban et al., 2011, Zelefsky et al., 2008) and two narrative reviews (Grimm et al., 2012, Schulz and Kagan, 2011) addressed this question.

**Low-risk**

All radiotherapy treatment options (EBRT and/or brachytherapy) are appropriate to be considered for patients with low-risk prostate cancer. Presently, high-intensity focused ultrasound (HIFU) and cryotherapy should be considered experimental, pending the results of future trials.

**Intermediate-risk**

All radiotherapy treatment options (EBRT and/or brachytherapy) are appropriate to be considered for patients with intermediate-risk prostate cancer. Hormonal therapy should be considered in addition to EBRT (D'Amico et al., 2004, Jones et al., 2011, Pilepich et al., 2001, Denham et al., 2011, D'Amico et al., 2011, Crook et al., 2004, Armstrong et al., 2011, Pisansky et al., 2013).

**High-risk**

Randomised trials have shown a benefit for active treatment in this group of patients (Warde et al., 2011, Widmark et al., 2009).

Combination treatment (EBRT and hormonal therapy) has a survival advantage over either modality alone (Warde et al., 2011, Widmark et al., 2009, Bolla et al., 2002, Lawton et al., 2005).

Retrospective results have shown good long-term results with a combination of EBRT, hormonal therapy and brachytherapy (Grimm et al., 2012).

There are no randomised data to suggest that radiotherapy and hormonal therapy is superior to surgery (with or without ART/SRT) for high-risk patients. Dose escalation has been shown to improve outcomes for intermediate- and high-risk prostate cancer (Kuban et al., 2011, Dearnaley et al., 2007, Zelefsky et al., 2008, Eade et al., 2007, Alicikus et al., 2011, Schulz and Kagan, 2011).

**Very-high-risk**

Two large randomised controlled trials have demonstrated a survival benefit for the combination of radiotherapy and hormonal therapy compared to hormonal therapy alone (Warde et al., 2011, Widmark et al., 2009).

Recommendation 2.8.2.1	Grade
<b>Low-risk</b> All radiotherapy treatment options are appropriate (EBRT and/or brachytherapy) to be considered for patients with low-risk prostate cancer.	<b>B</b>

<b>Recommendation 2.8.2.2</b>	<b>Grade</b>
<b>Intermediate-risk</b> All radiotherapy treatment options are appropriate (EBRT and/or brachytherapy) to be considered for patients with intermediate-risk prostate cancer.	<b>B</b>

<b>Recommendation 2.8.2.3</b>	<b>Grade</b>
<b>Intermediate-risk</b> Hormonal therapy should be considered in addition to EBRT.	<b>A</b>

<b>Recommendation 2.8.2.4</b>	<b>Grade</b>
<b>High-risk</b> Radiotherapy treatment options for patients with high-risk prostate cancer are EBRT in combination with hormonal therapy; EBRT and brachytherapy combinations; EBRT in combination with brachytherapy and hormonal therapy.	<b>B</b>

<b>Recommendation 2.8.2.5</b>	<b>Grade</b>
<b>Very-high-risk</b> A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients.	<b>A</b>

<b>Recommendation 2.8.2.6</b>	<b>Grade</b>
<b>Very-high-risk</b> A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients.	<b>C</b>

<b>Good practice point</b> Treatment options should be individualised for very high-risk patients.
<b>Good practice point</b> Prior to considering treatment, clinicians need to take into account individual co-morbidities, age, and life expectancy. All patients should be discussed at a multidisciplinary meeting and patients should be seen in consultation by both a urologist and a radiation oncologist.

**Clinical question 2.8.3**

**For men with prostate cancer what is defined as a biochemical recurrence after curative treatment?**

**Evidence statement**

International guidelines (NICE, 2014, Oncoline, 2007) are largely in agreement and reference the ASTRO 2005 definition as the most commonly used criteria for biochemical failure post radiotherapy.

A recurrence of prostate cancer can be defined as:

- Following radical prostatectomy, at least two PSA readings  $\geq 0.2\mu\text{g/L}$ ; and
- Following radiotherapy, a PSA value of  $2\mu\text{g/L}$  above the nadir after treatment.

The reduction in PSA after brachytherapy is often slow, and it can take more than five years to reach the PSA nadir (Grimm et al., 2001). The ASTRO criteria for PSA recurrence also apply to brachytherapy. Although the PSA nadir is an important factor, no absolute value can be established that indicates treatment success. PSA bounce after brachytherapy is often more pronounced than that seen after EBRT, and it can take up to 18 months before the PSA decreases again, often to a level lower than what was previously considered the nadir (Reed et al., 2003). (Oncoline, 2007)

Kuban et al., (2006) reported the most sensitive and specific practical definitions of biochemical recurrence after brachytherapy were the current nadir +  $1\mu\text{g/L}$  and the current nadir +  $2\mu\text{g/L}$ , respectively (ASTRO 2005). The sensitivity and specificity of the ASTRO 2005 definition were comparable to those seen in the radiotherapy cohort (Kuban et al., 2005, Horwitz et al., 2005). The ASTRO 2005 definition had a false call rate of 2% due to PSA bounce in a large series of men after EBRT or brachytherapy for prostate cancer (Pickles, 2006). (NICE, 2014)

It is important not to misinterpret PSA bounce as a biochemical recurrence following radiation especially brachytherapy. This phenomena tends to occur within two years after radiotherapy.

<b>Recommendation 2.8.3.1</b>	<b>Grade</b>
Following radical prostatectomy, a recurrence of prostate cancer can be defined as at least two PSA readings $\geq 0.2\mu\text{g/L}$ .	<b>C</b>

<b>Recommendation 2.8.3.2</b>	<b>Grade</b>
Following radiotherapy, a recurrence of prostate cancer can be defined as a PSA value of $2\mu\text{g/L}$ above the nadir after treatment.	<b>C</b>

<b>Good practice point</b>
It is important not to misinterpret PSA bounce as a biochemical recurrence following radiation especially brachytherapy. This phenomena tends to occur within one to two years after radiotherapy.



**Clinical question 2.8.4**

**For men with prostate cancer with a biochemical recurrence after curative treatment (in the absence of obvious metastatic disease), what additional treatments should be offered?**

**Evidence statement**

Guidelines from NICE (2014) and Oncoline (2007) addressed this question.

Randomised trials regarding the benefits of salvage radiotherapy and hormone therapy are ongoing. Retrospective data have shown a benefit for salvage radiation treatment.

Offer men with biochemical relapse after radical prostatectomy, with no known metastases, radical radiotherapy to the prostatic bed. There is a range of evidence to support this recommendation. (NICE, 2014)

Brachytherapy can also be used for the treatment of local recurrence following EBRT. Initial results suggest that the incidence of adverse events, such as irritative and obstructive micturition disorders, was low (Grado et al., 1999, Battermann, 2000). Results are likely optimal with an originally low PSA, Gleason score <7, stage ≤cT2 and a long interval between primary treatment and confirmation of local recurrence (>4 years). Long-term results, however, were not found and comparative studies have not been published. (Oncoline, 2007)

Hormonal therapy may control symptomatic, progressive or metastatic disease following either surgery or radiation. There are variations in practice with regard to the indications for, and the timings of, hormonal therapy in these situations. Other systemic therapies are being investigated in continuing clinical trials. (NICE, 2014)

Meta-analysis showed a small, but not statistically significant improvement in overall and disease specific survival at one, two and five years, in favour of early salvage EBRT. The review concluded that there was insufficient evidence about the use of androgen suppression in men with clinically localised disease, who experience biochemical recurrence without other signs or symptoms. Moul et al., (2004) considered the timing of hormonal therapy in a large case series of men with biochemical recurrence. There was no difference between the metastasis free survival of early and delayed hormonal therapy groups. A subgroup analysis, however, showed significantly better metastasis free survival for high-risk patients treated with early hormonal therapy. (NICE, 2014)

**Good practice point**

Salvage therapies should be considered when PSA rise is evident. Offer men with biochemical relapse after radical prostatectomy, with no known metastases, radical radiotherapy to the prostatic bed.

**Good practice point**

Salvage brachytherapy should be considered for selected patients with biopsy proven local recurrence.

**Good practice point**

Hormonal therapy is not routinely recommended for men with prostate cancer who have a biochemical relapse unless they have symptomatic local disease progression, or any proven metastases, or a PSA doubling time of <3 months.

**Clinical question 2.8.5****Which patients with prostate cancer will benefit from neoadjuvant or adjuvant hormone therapy in conjunction with radiotherapy?****Evidence statement**

A systematic review (D'Amico et al., 2012), eleven RCTs (Armstrong et al., 2011, Bolla et al., 2002, Bolla et al., 2009, Crook et al., 2004, D'Amico et al., 2011, Denham et al., 2011, Hanks, et al., 2003, Jones et al., 2011, Lawton et al., 2005, Pilepich et al., 2001, Pisansky et al., 2013) and a cohort study (D'Amico et al., 2004) addressed this question.

There is a lack of evidence to suggest that the addition of androgen deprivation therapy to radical radiotherapy is of benefit in patients with low-risk disease (Jones et al., 2011). For patients with intermediate-risk prostate cancer, ADT for four to six months should be considered in conjunction with EBRT (D'Amico et al., 2004, Jones et al., 2011, Pilepich et al., 2001, Denham et al., 2011, D'Amico et al., 2011, Crook et al., 2004, Armstrong et al., 2011, Pisansky et al., 2013). A pooled analysis suggests that a duration of six months is optimal (D'Amico et al., 2012). The options for patients with high-risk prostate cancer include a combination of radiation therapy and consideration for long term hormone androgen deprivation therapy (Bolla et al., 2002, Hanks et al., 2003, Bolla et al., 2009, Lawton et al., 2005) or EBRT plus brachytherapy with or without ADT. A combination of EBRT and long-term androgen deprivation therapy is recommended for patients with very high-risk disease (Bolla et al., 2002, Hanks et al., 2003, Bolla et al., 2009, Lawton et al., 2005).

<b>Recommendation 2.8.5.1</b>	<b>Grade</b>
<b>Low-risk</b> There is a lack of evidence to suggest that the addition of androgen deprivation therapy to radical radiotherapy is of benefit in patients with low-risk disease.	<b>C</b>
<b>Recommendation 2.8.5.2</b>	<b>Grade</b>
<b>Intermediate-risk</b> Androgen deprivation therapy for four to six months should be considered in conjunction with EBRT. A pooled analysis suggests that a duration of six months is optimal.	<b>A</b>
<b>Recommendation 2.8.5.3</b>	<b>Grade</b>
<b>High-risk</b> A combination of radiation therapy and consideration for long term hormone androgen deprivation therapy.	<b>A</b>
<b>Recommendation 2.8.5.4</b>	<b>Grade</b>
EBRT plus brachytherapy with or without androgen deprivation therapy.	<b>C</b>
<b>Recommendation 2.8.5.5</b>	<b>Grade</b>
<b>Very-high-risk</b> A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients.	<b>A</b>
<b>Recommendation 2.8.5.6</b>	<b>Grade</b>
A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients.	<b>C</b>

## 2.9 Palliative care

There is a HSE Clinical Programme for Palliative Care and a Needs Assessment Guide was published in 2014. Palliative care recommendations are included as a generic set of recommendations for the National Clinical Guideline.

**Clinical question 2.9.1****When should palliative care be introduced for patients with cancer?****Evidence statement**

Palliative care is an approach that improves the quality of life of people and their families facing the problems associated with life-limiting illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (World Health Organisation, 2014). It is a vital and integral part of all clinical practice.

When combined with standard cancer care or as the main focus of care, palliative care leads to better patient and caregiver outcomes. These include improvement in symptoms, quality of life (QOL), and patient satisfaction, with reduced caregiver burden. Earlier involvement of palliative care also leads to more appropriate referral to and use of hospice, and reduced use of futile intensive care (Smith et al., 2012).

No trials to date have demonstrated harm to patients and caregivers from early involvement of palliative care (Smith et al., 2012).

A 2013 literature review on the cost and cost-effectiveness of palliative care found that despite wide variation in study type, characteristic and study quality, there are consistent patterns in the results. Palliative care is most frequently found to be less costly relative to comparator groups, and in most cases, the difference in cost is statistically significant. (Smith et al., 2014)

Good clinical practice dictates that assessment of palliative care needs should be an ongoing process throughout the course of a patient's illness; assessments should be carried out at key transition points in the patient pathway, for example:

- At diagnosis of a life-limiting condition
- At episodes of significant progression/exacerbation of disease
- A significant change in the patient's family/social support
- A significant change in functional status
- At patient or family request
- At end of life. (HSE, 2014)

Palliative care services should be structured in three levels of ascending specialisation according to the expertise of the staff providing the service (Department of Health, 2001):

- **Level one (Palliative Care Approach):** Palliative care principles should be appropriately applied by all healthcare professionals.
- **Level two (General Palliative Care):** At an intermediate level, a proportion of patients and families will benefit from the expertise of healthcare professionals who, although not engaged full time in palliative care, have had some additional training and experience in palliative care.
- **Level three (Specialist Palliative Care):** Specialist palliative care services are those services whose core activity is limited to the provision of palliative care.

All patients should be able to engage easily with the level of expertise most appropriate to their needs.

Recommendation 2.9.1.1	Grade
For patients with cancer, early provision of palliative care can improve patient outcomes.	C

Recommendation 2.9.1.2	Grade
Assessment of palliative care needs should be an ongoing process throughout the course of a patient's cancer illness and services provided on the basis of identified need.	D

## **3 National Clinical Guideline development process**

### **3.1 Aim of National Clinical Guideline**

The overall objectives of this National Clinical Guideline are:

- To improve the quality of clinical care,
- To prevent variation in practice,
- To address areas of clinical care with new and emerging evidence,
- Be based on the best research evidence in conjunction with clinical expertise,
- Be developed using a clear evidence-based internationally used methodology.

### **3.2 Methodology and literature review**

The full methodological processes for this guideline are available in the full guideline version, which is available on the NCEC and NCCP websites.

The methodology for the development of the guideline was designed by a research methodologist and is based on the principles of Evidence-Based Practice (EBP) (Sackett et al., 2000). The methodology is described in detail in the NCCP Methodology Manual for guideline development.

#### **Step 1: Develop clinical questions**

The first step in guideline development was to identify areas of new and emerging evidence or areas where there was variance in practice. These questions then formed the basis for the types of evidence being gathered, the search strategy, and the inclusion and exclusion criteria.

To formulate the clinical questions they were broken down into their component parts using the PICO(T) framework:

- Participant/Population
- Intervention/Exposure
- Control/Comparison
- Outcome
- Time.

This process was carried out by discipline specific sub-groups. The GDG signed off the entire list of clinical questions to ensure a comprehensive guideline. The resulting 45 clinical questions are listed in appendix 4 of the full National Clinical Guideline.

#### **Step 2: Search for the evidence**

The first step in searching for the evidence is the identification of international guidelines. Searches of the primary literature were only conducted if the answers to the clinical questions were not found in up to date evidence based guidelines.

The clinical questions formulated in step one were used to conduct literature searches of the primary literature. The systematic literature review protocol was developed for the guideline development process by the HSE librarians in conjunction with the NCCP (see appendix 5 of the full National Clinical Guideline). The following bibliographic databases were searched in the order specified below using keywords implicit in the PICO(T) question and any identified subject headings:

- Cochrane Library
- Point-of-Care Reference Tools

- Medline
- Embase (where available)
- Other bibliographic databases such as PsycINFO, CINAHL, as appropriate.

The literature was searched based on the hierarchy of evidence. All literature searches were updated prior to publication and are current up to September 2014. A full set of literature search strategies is available on the NCCP and NCEC websites.

Details of the search strategy undertaken for the budget impact assessment are available in appendix 11 of the full National Clinical Guideline.

### **Step 3: Appraise the literature for validity and applicability**

International guidelines were appraised using the international, validated tool; the AGREE II instrument (Brouwers et al., 2010). Primary papers were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (SIGN).

There were three main points considered when appraising all the research evidence:

- Are the results valid? (internal validity)
- What are the results? (statistical and clinical significance)
- Are the results applicable/generalisable to the patient/population of the guideline? (external validity).

### **Step 4: Formulate and grade the recommendations**

The evidence which addressed each clinical question, both from international guidelines and primary literature, was extracted into evidence tables. Recommendations were formulated through a formal structured process. A 'considered judgment form' (adapted from SIGN; see NCCP Methodology Manual: Appendix VII) was completed for each clinical question.

The following items were considered and documented:

- What evidence is available to answer the clinical question?
- What is the quality of the evidence?
  - Is the evidence consistent?
  - Is the evidence generalisable to the Irish population?
  - Is the evidence applicable in the Irish context?
  - What is the potential impact on the health system?
- What is the potential benefit and potential harm to the patient?
- Are there resource implications?

The evidence statements and recommendations were then written. Each recommendation was assigned a grade by the GDG. The grade reflected the level of evidence upon which the recommendations were based, the directness of the evidence, and whether further research is likely to change the recommendation. The levels of evidence tables and grading systems used are in section 1.4.

Good practice points were based on the clinical expertise of the GDG.

For the economic literature, key messages are presented in boxes entitled 'relevance to the guideline recommendations'.

## **3.3 Financial impact of condition/disease**

Many recommendations in this guideline represent current standard practice and are therefore cost neutral. However, the GDG has identified the areas that require change to ensure

full implementation of the guideline. The potential resource implications of applying these recommendations have been considered. In areas where additional resources are required these will be sought through the HSE service planning process.

The complete budget impact assessment to support the recommendations of this National Clinical Guideline is described in the full version National Clinical Guideline, Appendix 11.

## **3.4 External review**

### **3.4.1 Patient advocacy**

A collaborative approach is used in the development of the NCCP patient information, clinical guidelines and other national projects. All NCCP booklets are submitted to the National Adult Literacy Agency (NALA) ([www.nala.ie](http://www.nala.ie)) for the Plain English Award. This is to ensure comprehension and readability are in line with health literacy best practice standards. Service user testing is a key part of the process, and includes liaising with the HSE Patient Forum, online surveys, and engaging with other relevant patient groups e.g. Irish Cancer Society, Marie Keating Foundation.

### **3.4.2 National stakeholder and international expert review**

The draft guideline was signed off by the entire GDG and the NCCP Guideline Steering Group before going to national stakeholder review. It was circulated to relevant organisations and individuals for comment between 30<sup>th</sup> May and 18<sup>th</sup> July 2014. A full list of those invited to review this guideline is available in appendix 7 of the full version National Clinical Guideline.

Stakeholders were asked to comment on the comprehensiveness of evidence used to form the recommendations. The views and preferences of the target population were sought by inviting patient advocacy groups. Stakeholders were required to submit feedback with supporting evidence on a form provided (NCCP Methodology Manual: Appendix VIII) along with a completed conflict of interest form. A time-period of six weeks was allocated to submit comments.

All feedback received was reviewed by the project manager and research team. Suggested amendments and supporting evidence were reviewed by the discipline specific sub-group and consensus reached to accept or reject the amendments. Amendments were rejected following discussion between members of the relevant subgroup(s) and in instances where no superior evidence was provided or no conflict of interest form was provided. All modifications were documented.

The amended draft guideline was then submitted for international expert review. The GDG nominated two international bodies to review the draft guideline. These reviewers were chosen based on their in-depth knowledge of the subject area and guideline development processes. The review followed the same procedure as the national stakeholder review. The guideline was circulated for comment between 25<sup>th</sup> August and 17<sup>th</sup> October 2014.

A log was recorded of all submissions and amendments from the national stakeholder review and international expert review process.

## **3.5 Procedure for update of National Clinical Guideline**

This guideline was published in June 2015 and will be considered for review by the NCCP in three years. Surveillance of the literature base will be carried out periodically by the NCCP. Any updates to the guideline in the interim period or as a result of three year review will be subject

to the NCEC approval process and noted in the guidelines section of the NCCP and NCEC websites.

### **3.6 Implementation of National Clinical Guideline**

The implementation plan is based on the COM-B theory of behaviour change (Michie et al., 2011), as outlined in the NCCP Methodology Manual. The implementation plan outlines facilitators and barriers to implementation (see appendix 8 of the full National Clinical Guideline).

The National Clinical Guideline will be circulated and disseminated through the professional networks who participated in developing and reviewing this document. The guideline will also be available on the NCCP and NCEC websites.

A multidisciplinary clinical team is responsible for the implementation of the guideline recommendations and a Lead Clinician for Prostate Cancer has been nominated in each Prostate Unit in the designated cancer centres. Recommendations have been divided into the key clinical areas of radiology and diagnosis, pathology, active surveillance, surgery, medical oncology, radiation oncology and palliative care.

All priorities in relation to prostate cancer care are agreed annually by the NCCP and are submitted to the annual HSE Service Plan, which is published on the HSE webpage.

A list of relevant tools to assist in the implementation of the National Clinical Guideline is available in appendix 3.

### **3.7 Roles and responsibilities**

This National Clinical Guideline should be reviewed by the multidisciplinary clinical team and senior management in the hospital to plan the implementation of the recommendations.

The CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the National Clinical Guideline and to ensure that all relevant staff are appropriately supported to implement the guideline. A Cancer Network Manager from the NCCP meets with each cancer centre on a quarterly basis for performance monitoring and service planning.

All clinical staff with responsibility for the care of patients with prostate cancer are expected to:

- Comply with this National Clinical Guideline and any related procedures or protocols,
- Adhere to their code of conduct and professional scope of practice as appropriate to their role and responsibilities, and
- Maintain their competency for the management and treatment of patients with prostate cancer.



### 3.8 Audit criteria

It is important that both the implementation of the guideline and patient outcomes are audited to ensure that this guideline positively impacts on patient care.

The following audit criteria will be monitored:

**Access**

Referrals to the rapid access prostate clinic shall be offered an appointment within 20 working days of the date of receipt of a letter of referral in the cancer centre.

**Time to Treatment**

For all patients diagnosed with a primary prostate cancer, the interval between the date of decision to treat and date of first surgical intervention, where surgery is the first treatment, shall be less than or equal to 30 working days.

**Multidisciplinary Working**

All patients who are diagnosed with prostate cancer shall be discussed at Multidisciplinary Team (MDT) meeting.

**Diagnosis**

The histology report following a prostate biopsy should be available within 10 working days of the procedure being carried out in 80% of cases.

**Radiotherapy**

New patients with a primary prostate cancer undergoing radical therapy will be treated within 15 working days of being deemed ready to treat.

**Surgery**

- For patients who have a radical prostatectomy for prostate cancer and the specimen is classified as a pathological stage pT2, the positive margin status should not exceed 15%.
- For patients who have a radical prostatectomy for prostate cancer and the specimen is classified as a pathological stage pT2, post-operative PSA at three months will be below detection levels in 90% of cases.
- For patients who have a radical prostatectomy for prostate cancer and the specimen is classified as a pathological stage pT3, the positive margin status should not exceed 40%.
- For patients who have a radical prostatectomy for prostate cancer and the specimen is classified as a pathological stage pT3, post-operative PSA at three months will be below detection levels in 70% of cases.

## Appendix 1: NCCP Guideline Development Group membership

### Terms of reference

To develop a national evidence-based clinical guideline for the diagnosis, staging and treatment of patients with prostate cancer. Full terms of reference are available in the NCCP Methodology Manual for guideline development.

### Membership of the Guideline Development Group Chair

Mr. David Quinlan                      Consultant Urologist, SVUH

### Members

#### Radiology and Diagnosis

Dr. Conor Collins                      Consultant Radiologist, SVUH  
 Dr. Colin McMahon (c)              Consultant Radiologist, SVUH  
 Mr. Paul Sweeney                      Consultant Urologist, MH (to Q4 2013)

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 Dr. Christian Gulmann              Consultant Histopathologist, BH  
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 Dr. Teresa McHale                      Consultant Histopathologist, GUH

#### Active Surveillance

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 Prof. Frank Sullivan                      Consultant Radiation Oncologist, GUH

#### Palliative Care

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**NCCP**

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Dr. Eve O'Toole	Guideline Methodologist

**Librarians**

Ms. Maria Carrigan	Librarian, SLH
Mr. Gethin White	Librarian, HSE East

**Conflict of Interest**

Dr. David Gallagher received travel expenses from Sanofi for attending the Genito-Urinary ASCO symposium and travel expenses from Roche-Pfizer for attending the ASCO symposium.

**Additional contributors****NCCP Research Staff**

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The NCCP is grateful to the following individuals who have contributed to the development of the guideline:

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Ms. Mary McCann	Publishing & Artwork Editor, NCCP

American Urological Association (AUA)  
 Centre for Behaviour Change, University College London  
 College of American Pathologists (CAP)  
 Dutch Urological Association (OncoLine)  
 European Association of Urology (EAU)  
 National Cancer Registry Ireland (NCRI)  
 National Comprehensive Cancer Network<sup>®</sup> (NCCN<sup>®</sup>)  
 National Institute for Health and Care Excellence (NICE)  
 Royal College of Pathologists (RCPATH)

## Appendix 2: NCCP Guideline Steering Group membership

### Terms of reference

To set strategic direction regarding the development of multidisciplinary/interdisciplinary evidence-based clinical practice guidelines for the diagnosis, staging and treatment of cancer. Full terms of reference are available in the NCCP Guideline Methodology Manual for guideline development.

### Membership of the NCCP Guideline Steering Group

The NCCP Guideline Steering Group provided governance for the development of the guideline. The members of the steering group are listed below. The GDG project managers were also present at meetings as observers.

#### Chair

Dr. Jerome Coffey	Interim National Director, NCCP (since Nov 2014)
Dr. Susan O'Reilly	National Director, NCCP (until Nov 2014)

#### Members

Dr. Jerome Coffey	NCCP Radiation Oncology Advisor & SLRON
Mr. Justin Geoghegan	Chair Hepatobiliary GI GDG, SVUH
Ms. Noreen Gleeson	Chair Gynaecological GDG, SJH & The Coombe
Dr. Mary Hynes	Deputy Director, NCCP
Prof. Arnold Hill	NCCP Surgical Advisor & BH
Dr. Maccon Keane	NCCP Medical Oncology Advisor & GUH
Dr. Marcus Kennedy	Chair Lung GDG, CUH
Mr. Brendan Leen	Regional Librarian, HSE South-East
Ms. Debbie McNamara	Chair Lower GI GDG, BH
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Ms. Eileen Nolan	Project Manager, Prostate Tumour Group, NCCP
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Dr. Margaret O'Riordan	Medical Director, ICGP (to May 2014)
Dr. Eve O'Toole	Guideline Methodologist, NCCP
Prof. John Reynolds	Chair Gastrointestinal GDG, SJH
Dr. Karen Ryan	Consultant in Palliative Medicine & Clinical Lead Clinical Programme for Palliative Care, SFH
Mr. David Quinlan	Chair Prostate GDG, SVUH

## **Appendix 3: Summary of tools to assist in implementation of National Clinical Guideline**

National Clinical Guidelines for Cancer – Methodology Manual. National Cancer Control Programme, 2014.

[Health Professional and Patient Information](#)

[NCCP GP Referral Guidelines](#)

[NCCP Chemotherapy Protocols](#)

NCCP Patient Booklet: Having your Prostate Checked: What you should know.  
[www.hse.ie/eng/services/list/5/cancer/profinfo/Prostate\\_Booklet\\_new.pdf](http://www.hse.ie/eng/services/list/5/cancer/profinfo/Prostate_Booklet_new.pdf)

NCCP Patient Booklet: Having your Prostate TRUS Biopsy: What you should know.  
[www.hse.ie/eng/services/list/5/cancer/patient/leaflets/](http://www.hse.ie/eng/services/list/5/cancer/patient/leaflets/)

National Policy on the Prevention and Management of Infection Post Trans Rectal Ultrasound (TRUS) Guided Prostate Biopsy 2014.  
[www.hse.ie/eng/services/list/5/cancer/pubs/guidelines/guidelines.html](http://www.hse.ie/eng/services/list/5/cancer/pubs/guidelines/guidelines.html)

The above literature is available on the NCCP website.

[Health Information and Quality Authority \(HIQA\). National Standards for Safer Better Healthcare](#)

[Centre for Evidence Based Medicine \(www.cebm.net\)](http://www.cebm.net)

[Improving Health: Changing Behaviour - NHS Health Trainer Handbook](#)

[UCL Centre for Behaviour Change\(www.ucl.ac.uk\)](http://www.ucl.ac.uk)

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Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*; 337.

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## Appendix 4: Glossary of Terms and Conditions

### Definitions within the context of National Clinical Guideline

Case Control Study	The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute, in each of the groups. (Oxford CEBM)
Case Series	A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. (NCI Dictionary)
Clinician	A healthcare professional such as a doctor involved in clinical practice.
Cohort study	A research study that compares a particular outcome (such as lung cancer) in groups of individuals who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke compared with those who do not smoke). (NCI dictionary)
External validity	The extent to which we can generalise the results of a study to the population of interest.
Internal validity	The extent to which a study properly measures what it is meant to measure.
Isotope Bone Scan	Bone scans use radionuclides to detect areas of the bone which are growing or being repaired. An isotope is a chemical which emits a type of radioactivity called gamma rays. A tiny amount of radionuclide is put into the body, usually by an injection into a vein. Cells which are most 'active' in the target tissue or organ will take up more of the isotope. So, active parts of the tissue will emit more gamma rays than less active or inactive parts.
Meta-analysis	A process that analyses data from different studies done about the same subject. The results of a meta-analysis are usually stronger than the results of any study by itself. (NCI dictionary)
Radical Retropubic Prostatectomy	Surgery to remove all of the prostate and nearby lymph nodes through an incision in the wall of the abdomen. (NCI dictionary)
Radical Transperineal Prostatectomy	Surgery to remove all of the prostate through an incision between the scrotum and the anus. Nearby lymph nodes are sometimes removed through a separate incision in the wall of the abdomen. (NCI dictionary)

Randomised trial	An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. (Oxford CEBM)
Systematic review	The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardized methods for selecting and assessing articles. A systematic review differs from a meta-analysis in not including a quantitative summary of the results. (Oxford CEBM)

A list of abbreviations and references used throughout this Guideline Summary are available in the full version of the guideline available at: <http://health.gov.ie/patient-safety/ncec/>.









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