Multi-disciplinary Team (MDT) Guidance for Managing Prostate Cancer

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PLEASE NOTE: THIS GUIDANCE IS AN INTERIM PUBLICATION AND IS SCHEDULED FOR IMMEDIATE REVIEW IN 2014 WHEN IT WILL ADDRESS THE UPDATED NICE GUIDELINE AND THE OUTCOME OF OTHER RELEVANT TECHNOLOGY APPRAISALS

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Abbreviations

3D-CRT: three-dimensional conformal radiotherapy

ADT: androgen deprivation therapy

ASAP: atypical small acinar proliferation

BF: biochemical failure

BPFS: Biochemical progression free survival

BPH: benign prostatic hyperplasia

CAB: combined androgen blockade

CHHiP: Conventional or Hypofractionated High Dose IMRT for Prostate Cancer

CI: confidence interval

CPA: cyproterone acetate

CPFS: clinical progression free survival

CT: computed tomography

DES: diethylstilbestrol

DFS: disease-free survival

DRE: digital rectal examination

EBRT: external beam radiation therapy

EPC: Early Prostate Cancer

ERSPC: European Randomised Study of Screening for Prostate Cancer

FFF: freedom from failure

FSH: follicle stimulating hormonE

GnRH: gonadotrophin-releasing hormone

HDR: high dose rate

HIFU: high-intensity focused ultrasound

HR: hazard ratio

HRPC: hormone-refractory prostate cancer

HT: Hormone therapy

IAD: intermittent androgen blockade

IGRT: image guided radiotherapy

IMRT: intensity modulated radiotherapy

ISUP: International Society of Urologic Pathology

IPSS: International Prostate Symptom Score

LDR: low dose rate

LH: luteinising hormone

LHRH: luteinising hormone releasing hormone

LTAD: long-term androgen deprivation

MDT: multi-disciplinary team

MRC: Medical Research Council

MRI: magnetic resonance imaging

MRS: magnetic resonance spectroscopy

NCCN: National Comprehensive Cancer Network

NICE: National Institute for Health and Clinical Excellence

ONJ: osteonecrosis of the jaw

OS: overall survival

OR: Odds ratio

PET: positron emission tomography

PFS: progression-free survival

PLCO: Prostate, Lung, Colorectal and Ovarian

ProtecT: Prostate Testing for Cancer and Treatment

PSA: prostate-specific antigen

PSADT: prostate-specific antigen doubling time

RANK: Receptor activator of nuclear factor kappa-B

RCT: randomised controlled trial

RECIST: Response Evaluation Criteria in Solid Tumors

SRE: skeletal-related events

STAD: short-term androgen deprivation

TRUS: transrectal ultrasound

TURP: transurethral resection of the prostate

CRPC: castration resistant prostate cancer

mCRPC : metastatic castration resistant prostate cancer

Integrated Care and the Multi-disciplinary Team (MDT)

- The concept of integrated care is becoming increasingly accepted as a way to overcome fragmentation of patient management and to provide a consistent treatment strategy across the MDT. It also creates an optimal structure that facilitates audit and peer review.
- Integration within the MDT is essential for patients with prostate cancer because the collaboration between MDT members (Table 1) is central to the treatment strategy, with ongoing support from the wider team to manage pain and the adverse effects of therapy. By being familiar with the complete spectrum of management strategies, the MDT can assist patients in making treatment decisions that are specific for their individual disease state, co-morbid conditions, age and lifestyle.

Table 1: The make-up of the MDT in the prostate cancer setting

• Urological surgeons	• Oncology and urology nurse specialists
• Clinical and medical oncologists	• Palliative care specialist
• MDT co-ordinator and secretarial support	• Histopathologists
• Radiologists	

- Moves to true integrated practice can add value in the following ways: [Integrated Care Network 2004]
  - Changing the identity or branding of a service to create more positive user responses and staff allegiances, enabling a clear break with the past.
  - Securing organisational efficiencies, for example, in the shape of shared support services, integrated management, innovative administrative processes and emerging hybrid roles.
  - Defining a focus for action that includes clearer processes of accountability and is less prone to distraction by wider organisational concerns.
  - Introducing more robust arrangements for team-working and leadership-working in challenging times.
  - Creating new opportunities for investment, for example, in IT systems, and opening access to new sources of funding.
- The algorithms presented in this guidance provide a single framework that is adapted for each major category of prostate cancer: localised, locally advanced and advanced (Figure 1).
- The treatment algorithms presented in this document (Figures 2–4) represent a management structure that goes beyond a simple co-ordinated system and will work most efficiently when the MDT is functioning as a single integrated unit.

Integrated care and clinical governance

- The effective functioning of the MDT and tailored care pathways for patients will support the (now routine) clinical governance procedures implemented throughout the NHS. Traditionally, clinical governance relates to a single organisation or service and this can raise challenges, with the recognition that patients require management across different organisations and services. Therefore, it is appropriate to apply the principles of clinical governance to individual patients or groups of patients.
- The focus should be on optimum patient satisfaction and care, rather than on performance of the NHS institution. The MDT and development of organised pathways ensures that the patient's journey is monitored and assessed as a single entity.

Approach within the MDT

Key questions for the MDT – Localised Prostate Cancer

- TNM stage?
- Gleason grade?
- Prostate-specific antigen (PSA)/PSA kinetics?
- Performance Status?
- Co-morbidity/life expectancy?
- Symptoms:
  - bowel
  - urine (IPSS score)
  - bone
- Sexual Function?
- Social Situation?
- Family History?
- Clinical Trials?

Diagnostic Tests

- Digital rectal exam (DRE)
- PSA
- Transrectal ultrasound
- (TRUS)/biopsy
- MRI/CT pelvic scan*
- Bone scan*

(*Not mandatory for low-risk patients)

Key points for discussion with the patient

- Prognosis with and without radical treatment?
- Treatment options?
- Treatment side-effects?
- Impact on quality of life?
- Importance of:
  - Sexual function?
  - Urinary function?
  - Bowel function?
  - Physical strength, energy?
  - Level of activity?
  - Accessibility to prescribed drugs?
  - Psychosocial impact on them and their family?
- Family history?
- Clinical trials?

Approach within the MDT

Key questions for the MDT – Locally Advanced Prostate Cancer

- TNM stage?
- Gleason grade?
- Prostate-specific antigen (PSA)/PSA kinetics?
- Performance Status?
- Co-morbidity/life expectancy?
- Symptoms:
  - bowel
  - urine (IPSS score)
  - bone
- Sexual Function?
- Social Situation?
- Family History?
- Clinical Trials?

Diagnostic Tests

- DRE
- PSA
- TRUS
- TRUS biopsy/Transperineal biopsy
- MRI/CT pelvic scan
- Bone scan
- Specialist imaging where indicated e.g. choline PET
- Consider lymph node sampling (if this will determine changes in management approach)

Key points for discussion with the patient

- Survival prognosis?
- Treatment options?
- Treatment side-effects?
- Impact on quality of life?
- Importance of:
  - Sexual function?
  - Urinary function?
  - Bowel function?
  - Physical strength, energy?
  - Level of activity?
  - Accessibility to prescribed drugs?
  - Psychosocial impact on them and their family?
- Family history?
- Clinical trials?

Approach within the MDT

Key questions for the MDT – Advanced Prostate Cancer

- TNM stage?
- Gleason grade?
- Prostate-specific antigen (PSA)/PSA kinetics?
- Performance Status?
- Co-morbidity/life expectancy?
- Symptoms:
  - bowel
  - urine (IPSS score)
  - bone
- Sexual Function?
- Social Situation?
- Family History?
- Clinical Trials?
- Palliative Care Referral?

Diagnostic Tests

- DRE
- PSA
- Limited? TRUS biopsy (to confirm histological diagnosis for future therapies – e.g. entry into clinical studies)
- Biochemistry screen
- Full blood count
- Bone scan
- Consider CT Chest / Abdomen; CT/MRI pelvis if it may influence management decisions and entry into future clinical trials

Key points for discussion with the patient

- Survival prognosis?
- Treatment options?
- Treatment side-effects?
- Impact on quality of life?
- Importance of:
  - Sexual function?
  - Urinary function?
  - Bowel function?
  - Physical strength, energy?
  - Level of activity?
  - Accessibility to prescribed drugs?
  - Psychosocial impact on them and their family?
- Family history?
- Clinical trials?

The MDT ***Meeting*** is an essential part of cancer management. However, there are often difficulties in identifying which patients to discuss and whether time allows for presentation of relapsed patients as well as new diagnoses, ensuring that their details and diagnoses are available, and keeping a record of decisions made at the meetings.

- MDTs have repeatedly been endorsed as the principal mechanism for ensuring that all relevant disciplines and professional groups contribute to, and participate in, decisions regarding the clinical management of patients [NICE 2002].
- MDT-working is positively related to a range of measures of effectiveness, including the quality of clinical care.
- It is important to emphasise the distinction between management and administration.
- A central concept of integrated care is to reinforce the role of the MDT (working as a single unit), but with enough clinical freedom to tailor management strategies to the needs of individual patients.
- Treatment strategies are influenced by the stage of disease and by an interaction between the risk of disease progression, survival and key patient characteristics, such as age, lifestyle and general health. The discussion of these factors is of crucial importance in determining the most appropriate way forward. For example, age and the presence of co-morbidities may be a restrictive factor when considering surgery.
- The case notes, pathology reports, test results and radiology for each patient must be available to be discussed at the meeting. The MDT must also ensure that the patient has the fullest possible role in determining treatment – the importance of this cannot be overstated. Patient preference should be discussed within the MDT. Although the majority of men with prostate cancer want to be involved in treatment decisions, an estimated one in five of all patients does not raise, or really understand, the potential issues and associated side-effects of treatments and alternatives that may be available to them [House of Commons Committee of Public Accounts 2006].
- The possibility of including a patient in a relevant clinical trial should be highlighted.

Approach to the Patient

The patient's expectations

The patient should have the right to discuss their treatment with appropriately trained members of the MDT

- After a diagnosis of prostate cancer, most men will want to have some involvement in the decisions concerning their care. The following aspects have been found to be important [Davison BJ, *et al* 2004]:
  - Honesty about the severity of the cancer and their prognosis
  - Discussion of the best treatment options
  - The clinician being up-to-date on ongoing and recent research
  - Disclosing all treatment options
  - How cancer may affect their daily functioning
- It is essential that the patient and healthcare professionals discuss the likelihood of adverse events associated with each treatment option and implications for their future lifestyle when determining management strategies.
- The patient and his partner, family and/or other carers should be fully informed about care and treatment options and therefore able to make appropriate decisions based upon the choices offered by their healthcare professionals. For example, the choice between radical treatment and active surveillance may be influenced by a patient's desire to retain sexual activity, physical energy and quality of life.
- Patients should be informed and advised regarding the available treatment options and the potential effects of these on their lifestyle and quality of life.

Discussing evidence with patients

There is a lack of evidence to guide how healthcare professionals can most effectively share clinical data with those patients facing treatment decisions. However, basing recommendations largely on relevant clinical studies and expert opinion, it is possible to achieve five communication objectives when framing and communicating clinical evidence.

1. Understand the patient's experience, expectations and preferences
2. Build partnerships with the patient and carer
3. Provide evidence and discuss uncertainties and side-effects
4. Present recommendations
5. Check for understanding and agreement

Assessment and Diagnosis

Screening

PSA screening remains a relatively contentious subject in the field of prostate cancer. Assessment of the value of a test, which is so widely disseminated in clinical practice, is a particular challenge. There is conflicting evidence regarding whether screening results in a reduction in mortality from the disease. As a consequence available evidence must be used to minimize the risk of harms and maximize the benefits for an individual man.

- Three ongoing large, randomised, controlled clinical trials are evaluating the value of PSA screening for prostate cancer: the European Randomised Study of Screening for Prostate Cancer (ERSPC) [Schroder FH, *et al* 2012], the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial in the US [Andriole GL, *et al* 2012] and the UK-based Prostate Testing for Cancer and Treatment (ProtecT) study [Rosario DJ, *et al* 2008]. The first reports from these trials have been published and have added further information to the PSA screening debate:
    - The PLCO study reported no mortality benefit with the combination of PSA screening and digital rectal examination (DRE) during a median follow-up of 13 years [Andriole GL, *et al* 2012]. However, this was not a trial of screening versus no screening, but rather of "systematic" versus "opportunistic" screening, and there were high rates of screening in the control group.
    - In contrast, the ERSPC trial found that PSA screening was associated with a 21% relative reduction in prostate cancer mortality at a median follow-up of 11 years, equivalent to the prevention of approximately 7 prostate cancer deaths per 10,000 men screened. This mortality benefit was associated with a high risk of overdiagnosis, with nearly 76% of men who underwent a biopsy following an elevated PSA value having no cancer detected on biopsy [Schroder FH, *et al* 2012].
    - ProtecT has demonstrated a benefit of repeat PSA testing in reducing the risk of high-grade prostate cancer in men with an initial PSA concentration of 3–20 ng/ml [Rosario DJ, *et al* 2008].
- Based on the results of these two large, randomised trials, the general consensus is that at present there is insufficient evidence for widespread mass screening for prostate cancer. However early detection (opportunistic screening) should be offered to the well-informed man Quality of life and cost-effectiveness analyses from the ERSPC and PLCO trials, along with mortality results from ProtecT are needed to help resolve the ongoing PSA screening debate.

Risk factors for prostate cancer

The risk factors for prostate cancer are generally well-documented, but are highlighted here for completeness of the Guidance.

- Age
    - Relatively rare in men under the age of 50 years.
    - Incidence increases in those over 60 years.
- Race
    - A higher incidence of the disease is seen in African-Caribbean, African-American and West African races. The UK PROCESS study demonstrated that black men in the UK have substantially greater risk of developing prostate cancer compared with white men [Ben-Shlomo Y, *et al* 2008]
    - Men of Chinese and Japanese origin have a lower incidence of disease [Delongchamps NB, *et al* 2006].

- Geography
  - The highest incidence of prostate cancer is currently seen in North America and Northern Europe.
- Family history
  - Men with a first-degree relative affected by prostate cancer have a relative risk of developing the disease themselves 2-fold greater than men with no relatives affected [Steinberg GD, *et al* 1990].
  - Those men with an affected second-degree relative have an increased relative risk of 1.7 of developing the disease.
  - Men with both a first- and second-degree relative affected have an increased relative risk of 8.8 of developing the disease.
  - A small subpopulation of individuals with prostate cancer (about 9%) has true hereditary prostate cancer. This is defined as three or more affected relatives or at least two relatives who have developed early onset disease, i.e. before age 55 [Hemminki K 2012].
  - There is also some evidence to show a link between an increased risk of prostate cancer where there is a family history of breast, ovarian, bladder or kidney cancer [Negri E, *et al* 2005].
  - The UK Familial Prostate Cancer Study is currently looking at the genetics of the disease with possible sites of interest lying on chromosomes 2, 5, Y and loss of heterozygosity at 10q and 16q.

Diagnostic tests

The main diagnostic tools for prostate cancer include digital rectal examination (DRE), serum prostate specific antigen (PSA), and transrectal ultrasound (TRUS). The definitive diagnosis depends on the histological verification of adenocarcinoma in prostate biopsy cores or operative specimens.

DRE

- The DRE remains valid as an initial method for assessing the prostate; however, DRE findings should not be regarded as a fail-safe test.

PSA

- PSA is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate.
- As an independent variable, PSA concentrations are a better predictor of cancer than suspicious findings on DRE or TRUS [Catalona WJ, *et al* 1994;Elgamal A-AA, *et al* 1996].
- PSA is organ specific but not cancer-specific. Therefore, serum concentrations of PSA can be elevated in the presence of benign prostatic hyperplasia (BPH), prostatitis and other non-malignant conditions. Furthermore, there is, as yet, no recommendation for the optimal PSA threshold value that most effectively avoids the detection of insignificant cancers that are unlikely to be life-threatening [Aus G, *et al* 2003; Aus G, *et al* 2004].
- While PSA concentrations generally increase with advancing disease stage, the ability of PSA levels to accurately predict pathological stage in any one individual is low [Hudson MA, *et al* 1989; Brawer MK & Lange PH 1989; Partic AW, *et al* 1990].

- Asymptomatic patients who request a PSA test should be counselled before the procedure for the following reasons [Dearnaley DP, *et al* 1999]:
    - Although the test may detect a cancer at a stage where curative treatment can be offered, PSA will fail to detect some early tumours.
    - A PSA test may detect early prostate cancer in an estimated 5% of men aged 50–65 years.
    - Treatment of early prostate cancer can put the patient at some risk of toxicity and may not necessarily improve life expectancy

Factors affecting PSA concentrations are summarised below.

Age and race

Table 2: Age-specific PSA (ng/ml) reference ranges, by race [DeAntoni EP, *et al* 1996]

Age (years)	White	Black	Latino	Asian
40–49	0–2.3	0–2.7	0–2.1	0–2.0
50–59	0–3.8	0–4.4	0–4.3	0–4.5
60–69	0–5.6	0–6.7	0–6.0	0–5.5
70–79	0–6.9	0–7.7	0–6.6	0–6.8

Biopsy/Transurethral Resection of the Prostate (TURP) can cause an increase in PSA for a variable time period (4–12 weeks) [Xu ZQ, *et al* 2002].

Prostatitis can cause an increase in PSA concentration, which can be reduced to within a normal range with antibiotic treatment [Tchetgen MB, *et al* 1997; Gamé X, *et al* 2003].

Prostate size – a benignly enlarged gland can influence PSA concentrations.

Infection – elevated PSA levels can be sometimes be seen with febrile urinary tract infections.

Free and complexed PSA should be understood. Catalona *et al*. conclude that percentage free PSA is most useful in men with a PSA concentration in the range 2–15 ng/ml (Table 3); the higher the percentage of free PSA the lower the probability of cancer [Catalona WJ, *et al* 1998].

Table 3: Probability of prostate cancer based on total and percentage free PSA [Catalona WJ, *et al* 1998].

	Probability of cancer (%)
Total PSA (ng/ml)	
0–2	~1
2–4	15
4–10	25
>10	>50
Free PSA (%)	
0–10	56
10–15	28
15–20	20
20–25	16
>25	8

PSA density i.e. $\frac{\text{PSA level (ng/ml)}}{\text{TRUS-determined prostate volume (ml)}}$

May be helpful in differentiating BPH from prostate cancer in patients who have a normal DRE with a PSA 4–10ng/ml. A PSA density >0.15 may suggest prostate cancer.

PSA velocity can be valuable in the follow-up of men with a normal PSA but prior negative biopsies. Velocity is measured by a change in PSA concentration in three consecutive measurements taken at 6-monthly intervals. A change in PSA concentration of >0.75 ng/ml per year is more likely to indicate prostate cancer than BPH. The usefulness of PSA velocity in those with a PSA concentration >10 ng/ml is unknown [Smith DS & Catalona WJ 1994].

Transrectal Ultrasound (TRUS)

- TRUS detects 50% more patients with prostate cancer than physical examination alone [Gustafsson O *et al* 1992; Mettlin C, *et al* 1996], but the ultrasonic appearance of prostate cancer is variable and only a very small number of cancers are detected if a DRE and PSA test are normal [Mettlin C, *et al* 1996; Jones WT & Resnick MI 1990; Ellis WJ, *et al* 1994]. Therefore, TRUS is mainly used to aid biopsy.

Biopsy and tumour grading

- The first elevated PSA level should not prompt an immediate biopsy. The PSA level should be verified after a few weeks by the same assay under standardised conditions (i.e. no ejaculation and no manipulations).
- Prostate biopsies are traditionally guided by TRUS. The alternative is to use a transperineal approach with template biopsies.
- The National Institute for Health and Clinical Excellence (NICE) Prostate Cancer Guideline recommends that the serum PSA level alone should not automatically lead to a prostate biopsy [NICE 2008]. It states that to help men decide whether to have a prostate biopsy, healthcare professionals should discuss with them their PSA level, DRE findings (including an estimate of prostate size) and co-morbidities, together with their risk factors (including increasing age and black African and black Caribbean ethnicity) and any history of a previous negative prostate biopsy.
- NICE further highlights that men and their partners or carers should be given information, support and adequate time to decide whether or not they wish to undergo prostate biopsy [NICE 2008]. Men will need to comprehend the potential risks (such as potentially living with a diagnosis of prostate cancer that is deemed clinically insignificant) and the benefits of prostate biopsy.
- Where TRUS-guided biopsy is indicated, a minimum of 10 biopsies (as recommended by The British Prostate Testing for Cancer and Treatment Study) [Donovan J, *et al* 2003] should be obtained, according to the volume of the prostate. Biopsies should be performed under local anaesthetic and antibiotic cover [Eskicorapci SY, *et al* 2004].
- For each biopsy site, the number of biopsies positive for carcinoma and the International Society of Urologic Pathology (ISUP) 2005 Gleason score should be reported [Epstein JI, *et al* 2005]. The amount of cancer in each core should also be recorded either in terms of cancer core length (mm) or proportion of core involvement (%) as this correlates with tumour volume, extraprostatic extension, and prognosis after prostatectomy [Grossklaus DJ, *et al* 2002].
- The indications for a repeat biopsy if the first biopsy is negative include: rising and/or persistently elevated PSA; suspicious DRE; atypical small acinar proliferation (ASAP); extensive (multiple biopsy sites) prostatic intraepithelial neoplasia
- Magnetic Resonance Imaging (MRI) may be used to identify the possibility of an anterior located tumour and also allow targeted biopsies of any suspicious or abnormal area [Lemaitre L, *et al* 2009].
- A European study has reported that a prostate cancer detection rate for the first set of biopsies is 24% and for the second set of biopsies after a negative initial set as 13% [Djavan B, *et al* 2005].31
- Complications of transrectal biopsy include macrohaematuria and haematospermia. Severe infections were initially reported in <1% of cases, but this rate has increased in the last few years as a consequence of the evolution of antibiotic resistance strains with more post-biopsy hospitalisations for infectious complications while the rate of non-infectious complications has remained stable [Loeb S, *et al*. 2011].
- In some patients, prostate biopsy may be performed using a transperineal, template guided technique as the preferred approach. Possible reasons for this include: previous repeated negative TRUS biopsies; clinical or radiological suspicion of a large anterior tumour; more accurate characterization of tumour location and extent in order to guide management and assess eligibility for inclusion into focal therapy trials.
- In these patients, the prostate is divided into 20 anatomical zones and each zone is biopsied at 5mm intervals in a systematic manner using a template grid to guide the biopsy needle placement. Typically this results in between 40-70 biopsies depending on the size of the prostate gland.

- The biopsies are reported in a similar manner to TRUS-guided biopsies, with Gleason score, cancer core length (mm) and proportion of core involvement (%) recorded for each zone.
- This information can also be conveyed in a visual format by creating a 'map' of the prostate that illustrates the Gleason score and extent of tumour in each individual zone.

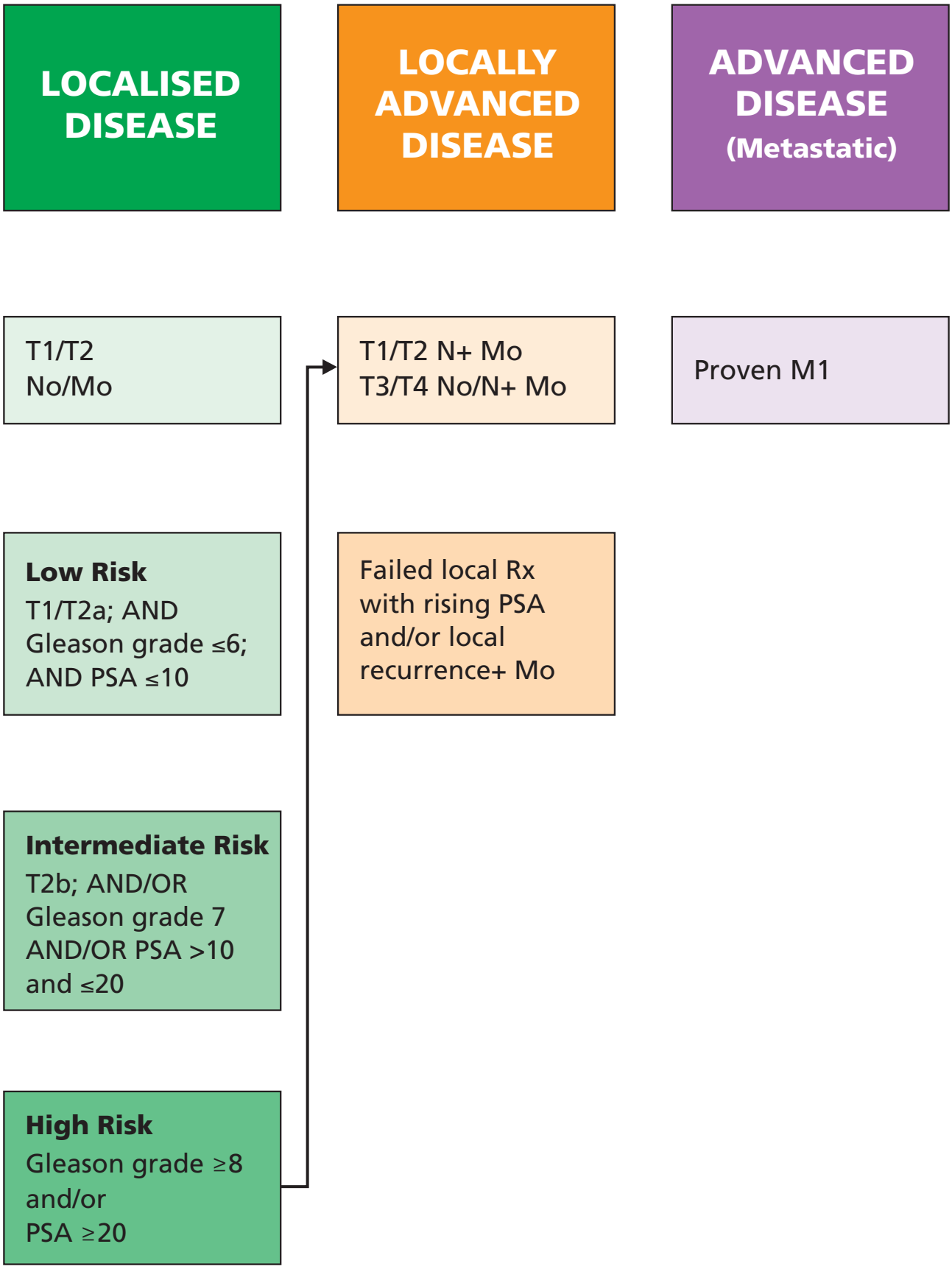
Magnetic Resonance Imaging (MRI)

- TNM staging, Gleason score, and PSA concentration facilitate estimation of the risk of extracapsular disease and lymph node metastases. Pelvic staging is required for those of high or intermediate risk (according to NCCN classification). MRI is the preferred option to stage pelvic lesions and where MRI is contraindicated, computed tomography (CT) should be used [NICE 2008].
- MRI is sensitive and specific in identifying extracapsular extension of prostate cancer in patients with high - or intermediate-risk disease [Allen DJ, *et al* 2004].
- NICE concludes [NICE 2008]:
    - MRI is now the most accurate and commonly-used imaging technique for tumour-staging men with prostate cancer. Many of the original publications on MRI technology are now considered to be outdated, and the accuracy reported for MRI is improving, typically with multiparametric, diffusion weighted scans
    - After transrectal prostate biopsy, intra-prostatic haematoma can affect image interpretation for at least 4-6 weeks.

Bone scans

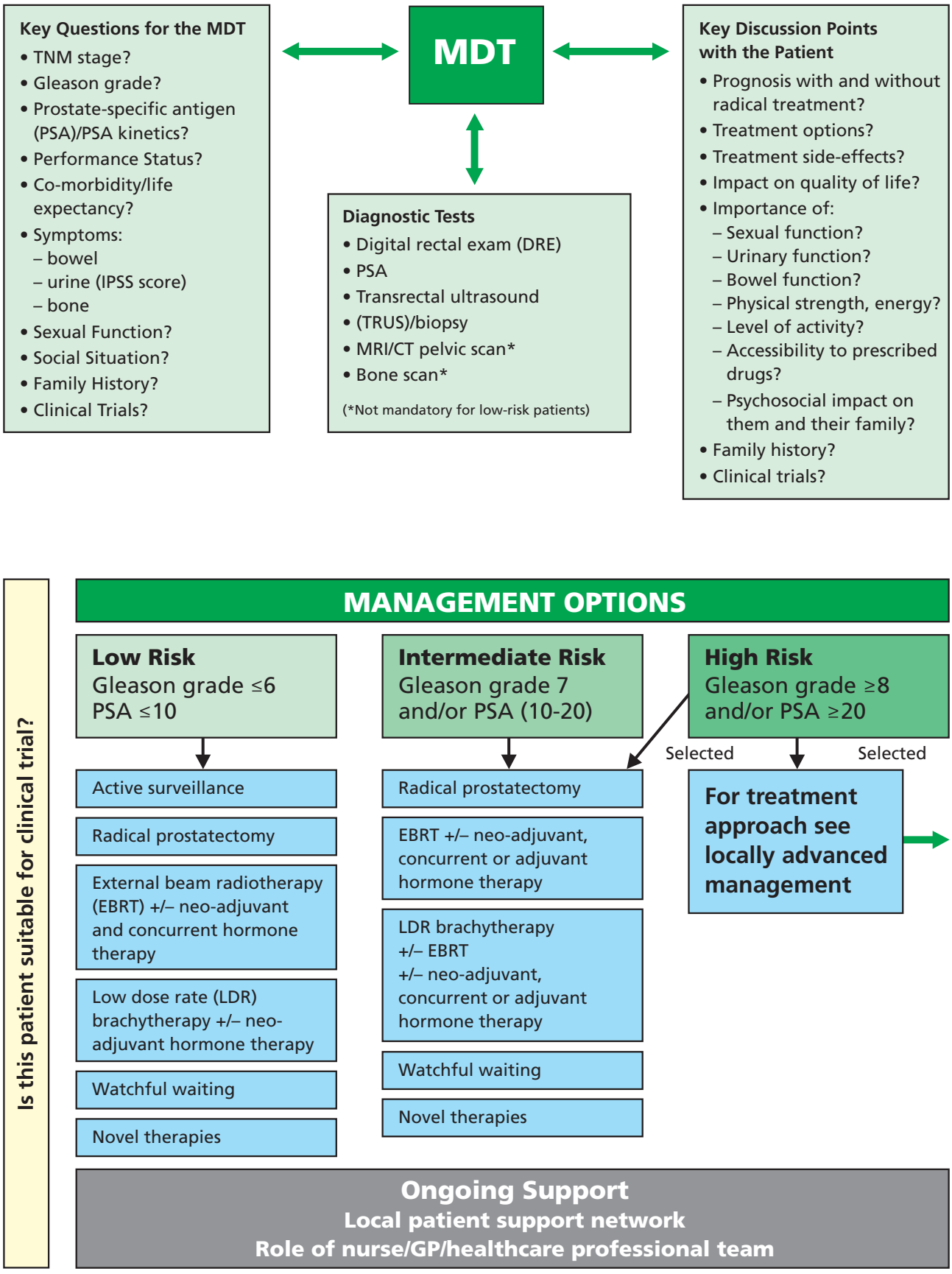
- Bone scans (particularly in patients with PSA concentration >20 ng/ml) are also important in the assessment process. A PSA concentration of <10 ng/ml is unlikely to indicate bone metastases at presentation. A PSA cut-off value of 10 ng/ml for men with Gleason grade ≤7 indicates a negative predictive value range of 91.5–100% [Gerber G & Chodak GW 1991].
- MRI can be an additional approach for distinguishing borderline metastases.

Figure 1: Summary of the definition of prostate cancer stages



Localised Disease: Management Options

Figure 2: Treatment algorithm for localised disease



The following guidance for managing localised prostate cancer focuses on low- and intermediate-risk categories, defined here as [D'Amico AV, *et al* 1998]:

- Low risk (T1/T2a; AND Gleason grade ≤6; AND PSA concentration ≤10 ng/ml)
- Intermediate risk (T2b; AND/OR Gleason grade 7 AND/OR PSA concentration: >10 and ≤20 ng/ml)

In the proposed management algorithms, high-risk localised disease falls more naturally into management of locally advanced disease.

Patient choice and the presence or absence of co-morbidities should be an essential component of management decisions in men with localised disease. Decisions concerning the choice of radical treatments need to be carefully balanced with the different options available and the impact of such treatments on a patient's co-morbidities.

In this section available evidence for the following management approaches is outlined:

- Active surveillance
- Watchful waiting
- Radical prostatectomy
- External Beam Radiation Therapy (EBRT)
- Low dose rate (LDR) brachytherapy
- Neoadjuvant/adjuvant hormone therapy
- Novel therapies

Active surveillance

Overview

- Active surveillance is an approach to the management of early prostate cancer in which the choice between curative treatment and observation is based on evidence of disease progression (PSA kinetics, repeat biopsy or MRI findings) during a period of close monitoring. The aim is to reduce the burden of treatment side-effects without compromising survival.
- Patients suitable for active surveillance are those with low-risk localised disease who are fit for radical treatment. Ongoing prospective studies of active surveillance have shown that 60–80% of such men will avoid the need for treatment, and that 99-100% prostate cancer-specific survival at 10 years is achievable [Selvadurai ED, *et al* 2013; van den Bergh RC, *et al* 2008].
- Active surveillance should be clearly distinguished from watchful waiting. Traditional watchful waiting involves relatively unstructured observation with late, palliative treatment for those who develop symptoms of progressive disease. In contrast, active surveillance involves close monitoring with early radical treatment in those with signs of disease progression.

Patient selection

- Low (or intermediate) risk, clinically localised prostate cancer
  - Clinical stage T1c/2a
  - Gleason grade ≤3+4
  - PSA concentration <15 ng/ml
  - Positive biopsies ≤50%
  - Age 50–80 years
  - Fit for radical treatment
- Active surveillance is particularly suitable for a subgroup of men with low-risk localised prostate cancer who have clinical stage T1c, a Gleason score of 3+3, a PSA density of <0.15 ng/ml per ml with <10 mm of any core involved [NICE 2008].

Side-effects

- Psychological uncertainty

Clinical evidence

- The case for active surveillance is based on the knowledge that PSA testing leads to significant overdiagnosis of prostate cancer. That is, approximately 50% of all cases detected as a result of PSA testing would never have been diagnosed in the absence of testing [Draisma G *et al* 2003]. It follows that treatment is 'unnecessary' in approximately half of all cases of PSA-detected prostate cancer.
- van den Bergh has reported the outcome of expectant management in 616 men who were diagnosed with prostate cancer between 1994 and 2007 at a mean age of 66.3 years in the ERSPC [van den Bergh RC, *et al* 2008]. All patients had low-risk disease with PSA <10 ng/ml, PSA density <0.2 ng/ml per ml, stage T1c/T2, Gleason score ≤3+3=6, and ≤2 positive biopsy cores. Median follow-up was 3.9 years. The 10-year prostate cancer-specific survival (21 patients at risk) was 100%, which sharply contrasted with 77% overall survival (OS), due to deaths from other causes.
- Selveduarai *et al*. reported the outcome of 471 men recruited to the Royal Marsden active surveillance study since 2002, at a median follow-up of 5.7 years [Selvadurai ED, *et al* 2013]. Median age was 66 years, and median initial PSA concentration 6.4 ng/ml. The 5-yr treatment-free probability was 70% (95% CI, 65–75%). There were two deaths from prostate cancer. Predictors of time to adverse histology were GS 7, PSAV >1 ng/ml per year, low ratio of free PSA to total PSA, and PPC >25%. There were two deaths from prostate cancer [Selvadurai ED, *et al* 2013].

Watchful waiting

Overview

- Watchful waiting is an approach to the management of localised prostate cancer that aims to avoid treatment, or delay it for as long as possible.
- Watchful waiting is particularly suitable for patients aged over 75 years or younger men with significant co-morbidities.
- Watchful waiting should be clearly distinguished from active surveillance. Conventional watchful waiting involves relatively unstructured observation with late, palliative treatment (usually hormone therapy) for those who develop symptoms of progressive disease. In contrast, active surveillance involves close monitoring with early, radical treatment in those with signs of progression.

Patient selection

- Asymptomatic clinically localised prostate cancer
  - Clinical stage T1–3 N0 M0
  - Gleason score ≤7
  - Any PSA concentration
  - Not suitable for radical treatment (usually by virtue of older age or co-morbidities)

Side-effects

- Uncertainty

Clinical evidence

- The NICE clinical guideline confirms a lack of evidence for watchful waiting and the Guideline Development Group reached a consensus that the recommendation from NICE would avoid unnecessary investigations [NICE 2008]:
  - Men with localised prostate cancer who have chosen a watchful waiting regimen and who have evidence of significant disease progression (rapidly rising PSA level or bone pain) should be reviewed by a member of the urological cancer MDT.

Radical Treatments

Radical Prostatectomy (RP)

Overview

- The procedure involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin. This can be accompanied by bilateral pelvic lymph node dissection. There are now four approaches to performing a radical prostatectomy: retropubic, perineal, laparoscopic and robotic. Laparoscopic and robotic approaches have the potential advantage of reduced blood loss and shorter inpatient stays.
- Selley *et al*. reviewed a total of 17 studies (two randomised controlled trials [RCTs] and 15 observational studies involving a total of 5410 patients) to investigate the efficacy of radical prostatectomy for men with localised prostate cancer. Cancer-specific survival after 10 years of follow-up ranged from 86% to 91%, with clinical disease-free survival (DFS) ranging from 57% to 83% [Selley S, *et al* 1997].

Patient selection

- Anaesthetic fitness
- At least 10 years' life expectancy

Side-effects

- Based on the systematic review by Selley *et al*., the following side-effects should be considered [Selley S, *et al* 1997]:
    - Operative and post-operative mortality: 0.2–1.2%
    - Sexual dysfunction: 51–61%
    - Incontinence (mild stress): 4–21%
    - Incontinence (total): 0–7%

Clinical evidence

- Two randomised trials have compared radical prostatectomy with watchful waiting in localised prostate cancer [Bill-Axelson A, *et al* 2011].
    - After a follow-up of 15 years, the SPCG-4 trial showed that RP was associated with a reduction of all-cause mortality: RR=0.75 (0.61 to 0.92). According to a post hoc statistical sub-group analysis, the number to treat (NNT) to avert one death was 15 overall and 7 for men younger than 65 years of age. Radical prostatectomy was also associated with a reduction in prostate cancer-specific mortality: RR=0.62 (0.44 to 0.87).
- This OS and CSS benefit could not be reproduced in another prospective randomised study [Wilt TJ, *et al* 2012]. After a median follow-up of 10 years, the PIVOT trial showed that RP did not significantly reduce all cause mortality: HR=0.88 (0.71 to 1.08); p=0.22, nor did RP significantly reduce prostate cancer mortality: HR=0.63 (0.36 to 1.09); p=0.09. According to a preplanned sub-group analysis among men with low-risk prostate cancer (n=296), RP non-significantly increased all-cause mortality: HR=1.15 (0.80 to 1.66). For men with intermediate-risk tumours (n=249), RP significantly reduced all-cause mortality: HR=0.69 (0.49 to 0.98). Among men with high-risk tumours (n=157), RP non-significantly reduced all-cause mortality: HR=0.40 (0.16 to 1.00).Among men with PSA > 10, RP significantly reduced all cause mortality: HR=0.67 (0.48 to 0.94).
    - Faced with these figures, some patients would choose surgery, but should also be given the option of conservative management with active surveillance [Singer PA, *et al* 1991].

Neoadjuvant and adjuvant hormone therapy with radical prostatectomy

- A review and meta-analysis of the role of Neoadjuvant Hormone Therapy (NHT) and RP has shown that this approach did not improve OS or DFS, but did significantly reduce positive margin rates [relative risk (RR): 0.49; 95% confidence interval (CI): 0.42-0.56, P < 0.00001), organ confinement (RR: 1.63; 95% CI: 1.37-1.95, P < 0.0001) and lymph node invasion (RR: 0.49; 95% CI: 0.42-0.56, P < 0.02) [Shelley MD, *et al* 2009]. Therefore, evidence suggests that the down-staging achieved with neoadjuvant hormone therapy does not translate into improved DFS, and therefore cannot be recommended outside of clinical trials [Bonney WW, *et al* 1999; Paul R, *et al* 2004; Selli C & Milesi C. 2004; Witjes WPJ, *et al* 1997].
- Similarly, there is currently no evidence that adjuvant hormone therapy provides a survival advantage for patients with pathologically proven localised disease [Hachiya T, *et al* 2002; Prayer-Galetti T, *et al* 2000]. A recent Cochrane review and meta-analysis studied the role of adjuvant HT following RP: the pooled data for 5-year OS demonstrated an odds ratio (OR) of 1.50 and 95% CI: 0.79-2.84 [Shelley MD, *et al* 2009]. Although this finding was not statistically significant, there was a trend favouring adjuvant HT. There was no survival advantage at 10 years.

Adjuvant radiotherapy after radical prostatectomy

- Extracapsular invasion (pT3), Gleason score > 7, and positive surgical margins (R1) can be associated with a risk of local recurrence and the role of adjuvant treatments for this high risk group is considered in the section of locally advanced prostate cancer and radical prostatectomy.

External Beam Radiotherapy (EBRT)

Overview

- Selley *et al*. reviewed 21 observational studies and one RCT involving radiotherapy and found that survival and recurrence rates are associated with grade and stage of the disease. The 5-year DFS for those with T1–T2 stage disease averaged 70–80%. Local progression was observed in 10–20% of these patients, while distant metastases were observed in 20–40% [Selley S, *et al* 1997].
- Nilsson *et al*. performed a systematic overview of radiotherapy in prostate cancer. Data from 26 non-randomised trials of conventional EBRT showed a 10-year DFS of 100%, 69% and 57% for T1a, T1b and T2 stage disease, respectively [Nilsson S, *et al* 2004].
- Long-term follow-up after EBRT continues to demonstrate an improvement in cause-specific survival. Improved selection and technical developments in radiotherapy leading to increased doses have shown better results.

Three-dimensional conformal radiotherapy (3D-CRT)

- There is evidence that increased radiation dose is associated with increased cancer cell kill for men with localised prostate cancer. However, the traditional two-dimensional technique of treatment planning and delivery is limited by the normal tissue toxicity of the surrounding structures (bladder, rectum and bowel), such that the dose that can be safely delivered to the prostate by EBRT is of the order of 64Gy in 2Gy per day fractions. Several technological advances over the last 20 years have enhanced the precision of EBRT, and have resulted in improved outcomes.
- The three-dimensional conformal radiotherapy (3D-CRT) approach reduces the dose-limiting late side-effect of proctitis [Dearnaley DP, *et al* 1999] and has allowed for dose escalation to the whole prostate to up to78 Gy.

Intensity Modulated Radiotherapy (IMRT)

- IMRT is an advanced technique which has superseded 3D-CRT. IMRT can modify the shape and intensity of the multiple radiotherapy beams. It is very precise in targeting the treatment area, sparing surrounding tissue and allowing dose escalation above 80Gy. IMRT is currently recommended, particularly for the irradiation of pelvic lymph nodes.

Dose escalation

- Several randomised studies have shown that dose escalation with 3D conformal radiotherapy and more recently with IMRT has a significant impact on the 5-year biochemical relapse free survival. However, no trials to date have shown an improvement in long term overall survival
- Evidence of the benefits of dose escalation has been demonstrated for T1–T3 prostate cancer by Pollack *et al*. in a phase III randomised study undertaken at the MD Anderson Hospital [Pollack A, *et al* 2002].
    - A total of 305 men were randomised between 1993 and 1998 to compare the efficacy of 70 Gy versus 78 Gy with a median follow-up of 60 months. The primary endpoint was freedom from failure (FFF), including biochemical failure, which was defined as three rises in PSA level.
    - The FFF rates for the 70 Gy and 78 Gy arms at 6 years were 64% and 70%, respectively (p=0.03). Dose escalation to 78 Gy preferentially benefited those with a pre-treatment PSA concentration >10 ng/ml; the FFF rate was 62% for the 78 Gy arm versus 43% for those who received 70 Gy (p=0.01). For patients with a pre-treatment PSA concentration ≤10 ng/ml, no significant dose-response relationship was found, with an average 6-year FFF rate of about 75%.
    - Although no difference in OS occurred, the freedom from distant metastasis rate was higher for those with PSA levels >10 ng/ml who were treated to 78 Gy (98% versus 88% at 6 years, p=0.056).
- Dearnaley and colleagues have reported their findings from the MRC RT01 study [Dearnaley DP, *et al* 2007].
    - In this 3D-CRT trial, 843 men were randomised to a standard dose of 64 Gy compared with an escalated dose of 74 Gy, with all men also receiving neoadjuvant hormone therapy.
    - Patients receiving the conventional dose had 5-year biochemical PFS rates of 60% compared to 71% in the dose-escalated arm. Advantages were also seen in terms of clinical PFS and the decreased use of androgen suppression.
    - An update of this study with 10 years of follow up has not shown any further benefit in biochemical PFS of 54% (172 events) versus 42% (224 events), HR 0.688 (0.56-0.84) p<0.0001 in favour of the dose escalated group [Dearnaley DP, *et al* 2011]. However, no overall survival benefit was demonstrated, with both the 64Gy and 74Gy arms having an overall survival of 70% HR 0.99 (0.77-1.28) p=0.337. The number of men requiring long term hormone therapy was reduced in the dose escalated arm HR 0.77 (0.59-1.00) p=0.05.
- Recently the long-term follow-up of the pilot study, which provided the initial safety and feasibility information for the national MRC RT01 trial have been published [Creak A, *et al* 2013].
    - In this study, 126 patients were randomised to a standard dose of 64 Gy compared with an escalated dose of 74 Gy after neoadjuvant androgen suppression.
    - After a follow up of 13.7 years, 49 of 126 patients restarted AS, 34 developed metastases and 28 developed CRPC. Median OS was 14.4 years.
    - Although escalated dose results were favourable, no statistically significant differences were seen between the randomised groups; PSA control (hazard ratio (HR): 0.77 (95% confidence interval (CI): 0.47–1.26)), development of CRPC (HR: 0.81 (95% CI: 0.40–1.65)), PC-specific survival (HR: 0.59 (95% CI:0.23–1.49)) and OS (HR: 0.81 (95% CI: 0.47–1.40)).
- The Dutch randomised phase III trial comparing 68 Gy with 78 Gy also demonstrated a significant increase in the 5-year rate of freedom from clinical or biochemical failure in patients treated with a higher dose of radiotherapy [Peeters ST, *et al* 2006]

- The phase III trial of the French Federation of Cancer Centres compared 70 Gy with 80 Gy in men with localised prostate cancer, in 306 patients with a low risk of pelvic lymph node involvement [Beckendorf V, *et al* 2011]. At a median follow up of 61 months, they demonstrated improved 5-year biological outcomes in favour of dose-escalated radiotherapy group. Using the Phoenix definition, the 5-year biochemical relapse rate was 32% and 23.5%, respectively (p = .09).
- Although these and other studies have shown benefits from dose escalation this has been offset to a degree by a reported increase in late rectal toxicity.
- Prospective non-randomised studies conducted at the Memorial Sloan Kettering cancer centre have compared the outcomes of 1100 men who received doses in the range of 64–70 Gy and 76–86 Gy using IMRT [Zelefsky MJ, *et al* 2001].
    - The results were evaluated within prognostic risk groups (using clinical stage, Gleason grade and presenting PSA concentration). They demonstrated that increasing the dose delivered beyond 70.2 Gy in men with intermediate- and high-risk disease improved the 5-year actuarial PSA relapse-free survival rate from 50% to 70% and 21% to 47%, respectively, in these two risk categories.
- IMRT has the potential to reduce late rectal toxicity as shown in a further study that reports 3-year actuarial ≥grade 2 gastrointestinal toxicity at 4% [Zelefsky MJ, *et al* 2002].
- A further development under investigation involves a change in the traditional fractionation schedules. Hypofractionation may improve cancer control for the same level of radiation-related toxicity and be a more effective treatment for prostate cancer with a predicted low alpha/beta ratio. Phase II dose escalation studies using shortened schedules of hypofractionated IMRT regimens have indicated acceptable early toxicity [Amer AM, *et al* 2003].
- The CHHiP (Conventional or Hypofractionated High Dose IMRT for Prostate Cancer) study is currently recruiting patients in the UK to compare standard fractionation IMRT (74 Gy in 37 fractions) to two hypofractionated IMRT regimens (60 Gy in 20 fractions or 57 Gy in 19 fractions) in combination with neoadjuvant hormone therapy [South CP, *et al* 2008]. There is no overall survival data available from this trial as yet but preliminary safety results have shown that hypofractionated high-dose radiotherapy seems equally well tolerated as conventionally fractionated treatment at 2 years

Image Guided Radiotherapy (IGRT)

- The advantages of dose escalation using IMRT means that organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity to the bladder, rectum and bowel. Techniques should therefore combine IMRT with some form of IGRT (fiducial markers, imaging), in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still under investigation.

Patient selection

- EBRT can be unsuitable for patients with bilateral hip replacement, previous radiotherapy, severe proctitis or bowel morbidity (such as ulcerative colitis or Crohns' disease).

Side-effects

- Acute complications include cystitis, faecal frequency and urgency, proctitis and rectal bleeding.
- Late complications occurring 3 months or later after treatment include impotence, bleeding, proctitis and diarrhoea.

EBRT plus neoadjuvant hormone therapy

- Neoadjuvant hormone therapy with an LHRH agonist can reduce the prostate volume by up to 30–40% [Shearer RJ, *et al* 1992;Forman JD, *et al* 1995] This can allow smaller treatment fields and as a result the level of toxicity experienced.
- There are also reports of an additive or synergistic effect on tumour cell kill with combined therapy. Theories as to the mechanism of this include improved oxygenation by reducing tumour bulk and movement of hormone-responsive cells into a resting phase, which could reduce repopulation rate and enhance tumour cell death (increased apoptosis) [Hara I, *et al* 2002].
- The RTOG 86-10 trial randomised 471 men with T2–T4 prostate cancer to radiotherapy +/– 4 months of androgen deprivation therapy (ADT) before and during EBRT or to radiotherapy alone [Pilepich MV, *et al* 2001].
    - At median follow-up of 8.7 years, there was a trend to improved survival (8-year survival 53% versus 44%, p=0.1) for those treated by hormone therapy with radiotherapy, which was significant for the subgroup with Gleason grade 2–6 disease (70% versus 52%, p=0.015) [Pilepich MV, *et al* 2001]..
    - Ten-year OS estimates (43% versus 34%) and median survival times (8.7 versus 7.3 years) favoured combined therapy with hormones and radiation compared to radiation treatment alone; however, these differences did not reach statistical significance (p=0.12).
    - There was a statistically significant improvement in 10-year disease-specific mortality (23% versus 36%; p=0.01), distant metastases (35% versus 47%; p=0.006), DFS (11% versus 3%; p<0.0001) and biochemical failure (65% versus 80%; p<0.0001) with the addition of neoadjuvant hormone therapy, but no differences were observed in the risk of fatal cardiac events [Roach M 3rd, *et al* 2008].
- The TROG 96.01 trial has shown that in the intermediate-risk patient group a 6-month course of ADT has shown some benefit when compared with a 3-month course [Denham JW, *et al* 2008].
    - Relative to radiation alone, the HR of prostate cancer-specific mortality from randomisation was 0.95 (95%CI: 0.63–1.41; p=0.79) in the 3-month ADT treatment arm and 0.56 (95%CI: 0.36–0.88; p=0.01) in the 6-month arm.
- A separate 6-month study compared 3D-CRT plus ADT and 3D-CRT alone [D'Amico AV, *et al* 2004].
    - After a median follow-up of 4.52 years, patients receiving 3D-CRT + ADT demonstrated a significantly lower prostate cancer–specific mortality rate (p=0.02).
    - 5-year OS rates were estimated at 88% (95%CI: 80–95) in the 3D-CRT + ADT group versus 78% (95%CI: 68–88) in the 3D-CRT group (p=0.04).

EBRT plus adjuvant hormone therapy

- Refer to section "EBRT plus adjuvant hormonal therapy" on pp 40.

Low dose rate (LDR) brachytherapy

Overview

- In 2005, NICE reviewed the medical literature on LDR brachytherapy and concluded that, in the absence of randomised trials, the results of LDR brachytherapy are comparable to those achieved with surgery or EBRT in well-selected patients [NICE 2005].
- Suitable patients include those with localised disease (up to T2a) with a Gleason grade ≤6, and a PSA concentration ≤10 ng/ml. Patients with significant urinary symptoms or post-TURP may not be suitable.
- Brachytherapy is as effective as radical prostatectomy in patients with low-risk localised disease [Crook J, *et al* 2001; Grimm P, *et al* 2012].
- In intermediate-risk localised disease, the comparison is less clear, because many studies have added EBRT in combination [Merrick GS, *et al* 2001].
- Brachytherapy is a single-step day case procedure following a spinal or general anaesthetic.

Brachytherapy plus EBRT

- In a matched-pair analysis, the 5-year biochemical failure-free survival rate was 86% for patients treated with EBRT and LDR brachytherapy, and 72% for patients treated with EBRT alone (p=0.03). Both treatments were associated with comparable incidences of late genitourinary side-effects (18-19%). Late rectal toxicity decreased by 15% in patients treated with EBRT and brachytherapy (p=0.0003). [Singh AM, *et al* 2005].

Brachytherapy plus neoadjuvant hormone therapy

- The role of neoadjuvant hormone therapy with brachytherapy is controversial. It is used to reduce the prostate volume when it exceeds 50 ml, in order to facilitate brachytherapy. Volume reduction decreases the total isotope activity required, potentially improves implant dosimetry and decreases pubic arch interference. [Potters L, *et al* 2005].

Patient selection (exclusions)

- Prostate size >50 ml
- Recent TURP
- Significant urinary outflow obstruction
- Previous AP resection
- Previous high dose pelvic radiotherapy

Side-effects

- A review of 16 studies by Crook *et al*. showed acute adverse events as [Crook J, *et al* 2001]:
  - Irritant urinary symptoms: 46–54%
  - Acute urinary retention: 1–14%
  - Acute proctitis: 1–2%
  - Chronic adverse events (reinforced by Wills & Hailey, 1999 [Wills F & Hailey D. 1991]:
    - Incontinence: 5–6%
    - Haematuria: 1–2%
    - Strictures: 1–2%
    - Proctitis: 1–3%
    - Erectile dysfunction: 4–14% (or up to 38% in Wills & Hailey, 1999 [Wills F & Hailey D. 1991] and up to 50% at 5 years in Merrick *et al*., 2001 [Merrick GS, B, *et al* 2001]).

Clinical evidence

- Very few comparative studies to date have evaluated the results of treatment options for prostate cancer using the most sensitive measurement tools. PSA has been identified as the most sensitive tool for measuring treatment effectiveness. To date, comprehensive unbiased reviews of all the current literature are limited for prostate cancer. A large scale comprehensive review of the literature comparing risk stratified patients by treatment option and with long-term follow-up was carried out by Grimm *et al* 2012 [Grimm P, *et al* 2012]. The results of the studies were weighted, respecting the impact of larger studies on overall results. The review identified a lack of uniformity in reporting results amongst institutions and centres. A large number of studies had been conducted on the primary therapy of prostate cancer but very few randomised controlled trials had been conducted. The comparison of outcomes from individual studies involving surgery (radical prostatectomy or robotic radical prostatectomy), external beam radiation (EBRT) (conformal, intensity modulated radiotherapy, protons), brachytherapy, cryotherapy or high intensity focused ultrasound remains problematic due to the non-uniformity of reporting results and the use of varied disease outcome endpoints. Technical advances in these treatments have also made long-term comparisons difficult. This international group conducted a comprehensive literature review to identify all studies involving treatment of localised prostate cancer published during 2000-2010. Over 18,000 papers were identified and a further selection was made based on the following key criteria: minimum/median follow-up of 5 years; stratification into low-, intermediate- and high-risk groups; clinical and pathological staging; accepted standard definitions for prostate-specific antigen failure; minimum patient number of 100 in each risk group (50 for high-risk group). A statistical analysis of the study outcomes suggested that, in terms of biochemical-free progression, brachytherapy provided superior outcome in patients with low-risk disease. For intermediate-risk disease, the combination of EBRT and brachytherapy appears equivalent to brachytherapy alone. For high-risk patients, combination therapies involving EBRT and brachytherapy plus or minus androgen deprivation therapy appear superior to more localized treatments such as seed implant alone, surgery alone or EBRT.
- A significant correlation has been demonstrated between recurrence rates and the implanted dose [Stock RG, *et al* 1998]. It has been shown that men receiving a D90 of > 140 Gy had a significantly higher biochemical control rate (PSA < 1.0 ng/mL) at 4 years than those who received less than 140 Gy (92% vs. 68%).

- Kupelian *et al*. studied 2991 consecutive patients with T1/T2 tumours treated with radical prostatectomy, LDR brachytherapy, EBRT or a combination of EBRT and brachytherapy. Biochemical relapse-free survival was similar in all groups when EBRT <72 Gy was excluded [Kupelian PA, *et al* 2004].
- Potters *et al* studied 1,449 consecutive patients treated with permanent prostate brachytherapy between 1992 and 2000. The mean pre-treatment PSA of 10.1ng/ml and 55% presented with Gleason 6 prostate cancer and 28% Gleason 7 disease. 400 patients (27%) were treated with neoadjuvant hormones and 301 (20%) were treated with combination EBRT. At a median follow up of 82 months, the overall and disease specific survival at 12 years was 81% and 93%, respectively. The 12-year biochemical free recurrence rates varied between 77% and 81% depending on the method of reporting recurrence. They concluded from multivariate analyses that implant dosimetry remains an important predictor for biochemical recurrence and that the addition of adjuvant hormone therapy or external radiation had an insignificant effect. [Potters L, *et al* 2005].

Novel therapies

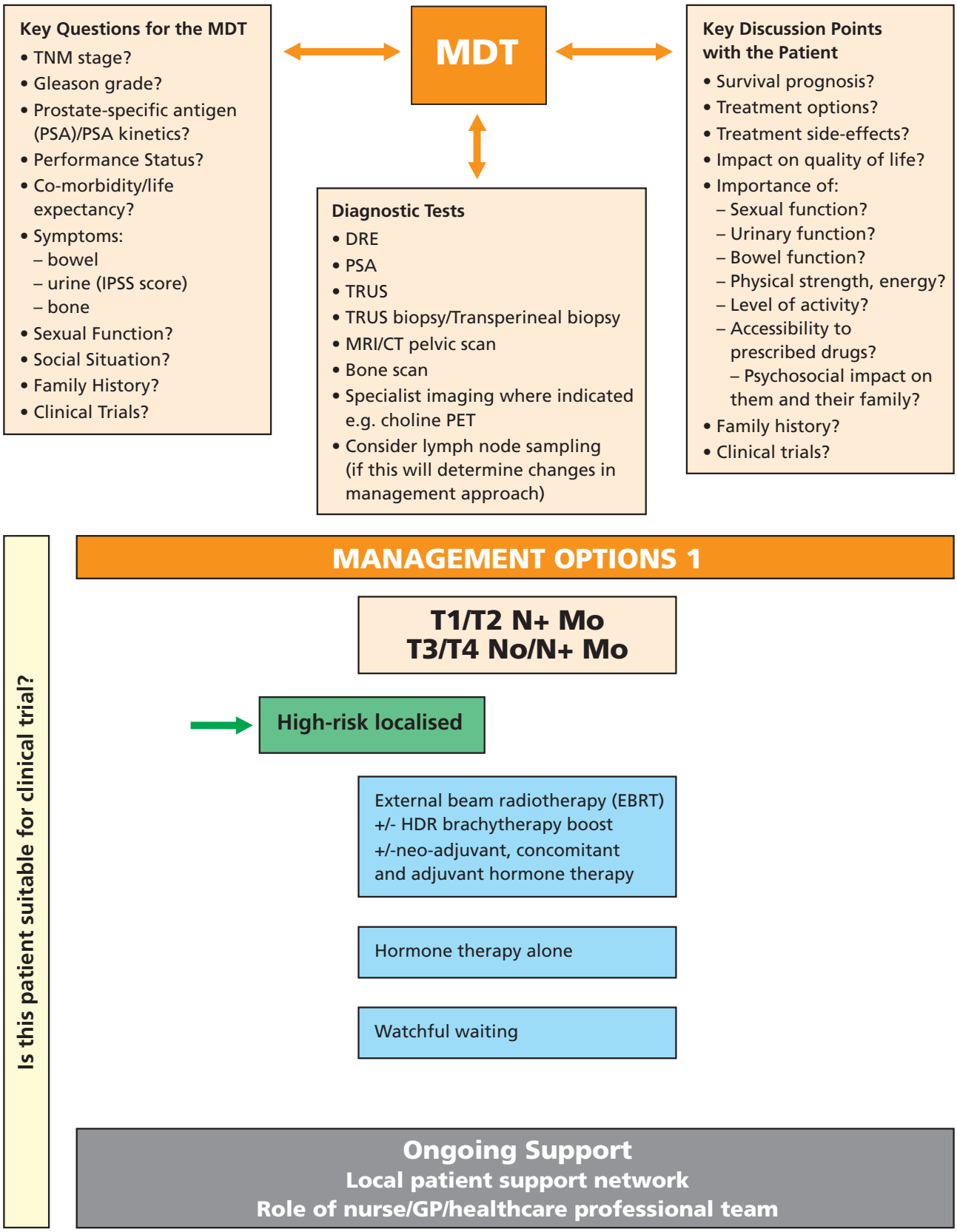
Cryotherapy/High-Intensity Focused Ultrasonography (HIFU)

The development of third-generation prostate cryotherapy has allowed the introduction of ultra-thin needles to deliver a minimally-invasive treatment for prostate cancer patients in the primary and salvage setting.

- Long *et al*. have performed a retrospective analysis of the multicentre, pooled, results of 975 patients treated with cryotherapy [Long JP, *et al* 2001]. The patients were stratified into three risk groups. Using PSA thresholds of 1.0 ng/mL and < 0.5 ng/mL and had a mean follow-up of 24 months. The 5-year actuarial biochemical disease free survival rates were:
    - 76% and 60%, respectively, for the low-risk group
    - 71% and 45%, respectively, for the intermediate-risk group
    - 61% and 36%, respectively, for the high-risk group
- Bahn *et al*. [Bahn DK, *et al* 2002], have reported the results of 7 year follow up on 590 patients treated with cryotherapy for clinically localised and locally advanced PCa. Using a PSA cut-off response level of < 0.5 ng/mL, the 7-year biochemical disease free survival for low-, medium- and high-risk groups was 61%, 68% and 61%, respectively.
- Longer-term follow-up series show biochemical DFS at 10 years of 80.56% for low-risk, 74.16% for moderate-risk and 45.54% for high-risk prostate cancer patients
- The toxicity from cryotherapy has reported erectile dysfunction in approximately 80% of patients and remains a consistent complication of the procedure, regardless of the generation of the system used. The complication rates described in third generation cryosurgery include tissue sloughing in about 3%, incontinence in 4.4%, pelvic pain in 1.4% and urinary retention in about 2% [De La Taille A, *et al* 2000]. Around 5% of all patients require transurethral resection of the prostate (TURP) for subvesical obstruction.
- This treatment has been approved by the American Urological Association and the European Association of Urology for treatment of patients with primary and radiation-failed prostate cancer
- In the NICE guidelines, the minimally-invasive treatments of cryosurgery and HIFU were considered to be experimental and for use only within the clinical trial setting [NICE 2008].
- Poissonnier reported on 227 patients with localised prostate cancer who were treated with HIFU at a single institution. The projected 5-year biochemical disease free survival rate was 66%, or 57% for patients with a pre-treatment PSA value of 4-10 ng/mL after a mean follow up of 27 months (range: 12-121) [Poissonnier L, *et al* 2007]
- Blana *et al*. have reported the results of 163 patients treated with HIFU for clinically organ confined prostate cancer. The actuarial disease free survival rate at 5 years was 66%, with salvage treatment initiated in 12% of patients [Blana A, *et al* 2008].
- In another study, 517 men with organ-confined or locally advanced PCa were treated with HIFU .Biochemical failure was defined as the PSA nadir + 2 ng/mL, After a median follow-up of 24 months, the biochemical disease free survival was 72% for the entire cohort. The biochemical disease free survival rates for low-, intermediate- and high-risk groups at 5 years was 84%, 64% and 45%, respectively (P < 0.0001) [Uchida T, *et al* 2009].
- Urinary retention appears to be one of the most common side effects of HIFU, with stress incontinence occurring in about 12% of patients. Subsequent TURP or bladder neck incision to treat subvesical obstruction can be used to treat these symptoms and is sometimes performed at the time of HIFU. Postoperative impotence has been reported in 55-70% of patients.

Locally Advanced Disease: Management Options

Figure 3: Treatment algorithm for locally advanced disease



The term 'locally advanced prostate' cancer can be used to encompass a spectrum of disease profiles that may include any of the following:

- Clinical stage T3, T4 or N1 cancers without evidence of distant metastases (M0)
- Clinical stages T1 and T2 ('localised') at diagnosis, where 'high-risk' features (PSA concentration ≥20 ng/ml or Gleason grade ≥8) indicate the likelihood of extraprostatic invasion or clinically undetectable metastatic disease.
- Pathological stage pT2 or pT3 disease with 'high-risk' features due to upstaging from additional pathological information after radical prostatectomy.

Men with locally advanced or high-risk prostate cancer generally have a significant risk of disease progression and cancer-related death if left untreated. These patients present two specific challenges. There is a need for local control and also a need to treat any microscopic metastases likely to be present but undetectable until disease progression. The optimal treatment approach will often therefore utilise multiple modalities. The exact combinations, timing and intensity of treatment continue to be strongly debated. Management decisions should be made after all treatments have been discussed by the MDT and the balance of benefits and side effects of each therapy modality have been considered by the patient with regard to their own individual circumstances.

Watchful waiting (deferred or immediate hormone therapy)

The waiting ('deferred treatment' or 'symptom-guided treatment') should be distinguished from active surveillance which involves close monitoring with early, radical treatment in those with signs of disease progression. Watchful waiting by contrast involves relatively unstructured observation with late, palliative treatment for those who develop symptoms of progressive disease.

Overview

- A pooled analysis of data from 2 RCTs involving 1036 men with locally advanced disease not suitable for curative treatment (T2–T4) suggested no survival benefit for immediate versus delayed hormone therapy at 1, 5 or 10 years [Wilt T, *et al* 2001].

Clinical evidence

- Adolfsson *et al*. prospectively followed 50 patients with locally advanced prostate cancer who were only treated upon patient request or when they became symptomatic. All patients were followed-up for more than 144 months, or had died before that point. OS and DFS at 5, 10 and 12 years was 68% and 90%, 34% and 74%, and 26% and 70%, respectively [Adolfsson J, *et al* 1999].
- Immediate versus deferred treatment for advanced prostate cancer was investigated by the MRC Prostate Working Party Investigators Group. An RCT of 943 men with asymptomatic metastases or locally advanced disease, not suitable for curative treatment, was undertaken, with randomisation to immediate or deferred hormone therapy [MRC Prostate Working Party Investigators Group 1997].
    - There was a significant advantage in the immediate treatment group in terms of distant progression. Mortality was only significantly changed by treating immediately in those with M0 disease (Table 5).
    - A modest but statistically significant increase in OS was seen in the immediate treatment group, but no significant difference in prostate cancer mortality or symptom-free survival was demonstrated.

- Due consideration must therefore be given to potential effects of long-term ADT versus the potential avoidance of such effects in patients if hormone therapy is deferred [Studer UE, *et al* 2008].

Table 5: Effect of immediate versus deferred hormonal treatment [MRC Prostate Working Party Investigators Group 1997]

		Immediate	Deferred
Distant progression		26%	45%
Mortality due to prostate cancer	M0 disease M1 disease	31.6% No significant difference	48.8% No significant difference

- A prospective randomised clinical phase III trial (EORTC 30981) by Studer UE *et al*, randomised 985 patients with T0-4 N0-2 M0 prostate cancer to immediate hormone or hormone treatment on the development of symptomatic disease progression [Studer UE, *et al* 2008]. After a median follow-up of 7.8 years, the overall survival hazard ratio was 1.25 (95% confidence interval [CI]: 1.05-1.48; non-inferiority $p > 0.1$) favouring immediate treatment. This appeared to be due to fewer deaths of non-prostatic cancer causes ($p = 0.06$). There was no difference in the time from randomisation to progression of hormone-refractory disease or prostate cancer-specific survival. The median time to the start of deferred treatment after study entry was 7 years. The conclusion suggested that immediate hormone therapy resulted in a modest but statistically significant increase in overall survival, but that there was no significant difference in prostate cancer mortality or symptom-free survival.
- The multicentre, International Early Prostate Cancer (EPC) study evaluated the efficacy and tolerability of adding the non-steroidal anti-androgen bicalutamide 150 mg once-daily to standard care (prostatectomy, radiotherapy or watchful waiting). 8,113 patients with localised or locally advanced non-metastatic prostate cancer were included [Iversen P, *et al* 2010].
  - Objective PFS and OS were defined as the primary endpoints. At a fourth analysis, the median follow-up was 9.7 years. Exploratory analyses were also conducted to determine the efficacy of bicalutamide in clinically relevant subgroups.
- A significant improvement in objective PFS in favour of bicalutamide 150 mg for all locally advanced disease patients was demonstrated. For those men with locally advanced disease who were managed by watchful waiting, there was a significant difference in PFS. The median time to progression was 6.6 years for those randomised to bicalutamide 150 mg compared to 3.7 years for those randomised to placebo. Patients in the watchful waiting subgroup showed a trend towards improved overall survival, this was statistically significant in sub-study 025 (carried out in Scandinavian in 1218 patients) HR=0.76 (0.59, 0.98) p=0.031 but did not reach significance in sub-study 24 (carried out in Europe, South Africa, Australia, Israel, and Mexico in 3603 patients) HR=1.03 (0.77, 1.37) p=0.844 [Iversen P, *et al* 2010].

Hormone therapy versus radiotherapy and hormone therapy

- A study by Widmark *et al* has shown that the addition of radiotherapy to hormone therapy for men with locally advanced or high-risk prostate cancer halves the 10-year prostate cancer-specific mortality and substantially decreases overall mortality [Widmark A, *et al* 2009].
    - This phase III study comparing endocrine therapy with and without local radiotherapy randomised 875 patients with locally advanced prostate cancer (T3; 78%; PSA concentration <70 ng/ml; N0; M0) to hormone therapy alone (3 months of total androgen blockade followed by continuous endocrine therapy using flutamide), or to the same hormone treatment combined with radiotherapy.
    - After a median follow-up of 7.6 years, 79 men in the hormone therapy group and 37 men in the hormone therapy plus radiotherapy group had died of prostate cancer. The cumulative incidence at 10 years for prostate cancer-specific mortality was 23.9% in the hormone alone group and 11.9% in the hormone therapy plus radiotherapy group (difference 12.0%; 95%CI: 4.9–19.1).
    - The 10-year cumulative incidence for overall mortality was 39.4% in the hormone therapy group and 29.6% in the hormone therapy plus radiotherapy group (difference 9.8%; 95%CI: 0.8–18.8).
    - The 10-year cumulative incidence for PSA recurrence was substantially higher in men in the hormone therapy group (74.7% versus 25.9%; HR 0.16; 95%CI: 0.12–0.20; p<0.0001).
    - After 5 years, urinary, rectal, and sexual problems were slightly more frequent in the hormone plus radiotherapy group.
- The National Cancer Institute of Canada (NCIC)/UK Medical Research Council (MRC)/Southwest Oncology Group (SWOG) intergroup PR3/PR07 study included 1,205 patients with stage T3-4 (n = 1057) or stage T2 with additional high risk features i.e. PSA > 40 ng/mL, or PSA > 20 ng in addition to Gleason Score > 8 and N0-X M0 prostate cancer [Warde, P, *et al* 2011]. These patients were randomly assigned to lifelong hormone therapy (bilateral orchidectomy or LHRH agonist), with or without radiotherapy (65-70 Gy to the prostate, with or without 45 Gy to the pelvic lymph nodes). The addition of radiotherapy to lifelong hormone treatment at a median follow up of 6 years demonstrated a reduced the risk of death from any cause by 23% (P = 0.03) and the risk of death due to prostate cancer by 46% (P = 0.0001) [Warde, P, *et al* 2011].

Side-effects of Hormone Therapy

- LHRH agonists: side-effects include erectile dysfunction and loss of libido, reduction in bone mineral density, hot flushes and sweating, and weight gain and metabolic effects.
- Bicalutamide (anti-androgens): side-effects include gynaecomastia and breast tenderness.
    - Mild to moderate gynaecomastia and breast pain are the most common adverse events described [McLeod DG, *et al* 2006].

External beam radiotherapy (EBRT) +/– neoadjuvant, concomitant and adjuvant hormone therapy

Radiotherapy Alone

- In locally advanced disease, EBRT alone has been shown to have a poorer outcome than in localised prostate cancer. Consequently, combination therapy with radiotherapy and hormone therapy is accepted as standard practice.
- Although it has been widely used, there are still many uncertainties associated with radical radiotherapy with regard to the optimum dose and field size (particularly to what extent the treatment volume should try to include pelvic lymph nodes). The advent of 3D Conformal radiotherapy (3D-CRT) and Intensity Modulated Radiotherapy (IMRT) in combination with Image Guided Radiotherapy (IGRT) has allowed the radiation field to be more precisely targeted to the tumour volume, thereby potentially reducing the side-effects of treatment and possibly allowing dose escalation that enhances its local efficacy.

Three-dimensional conformal radiotherapy (3D-CRT)

- There is evidence that increased radiation dose is associated with increased cancer cell kill for men with localised prostate cancer. However, the traditional two-dimensional technique of treatment planning and delivery is limited by the normal tissue toxicity of the surrounding structures (bladder, rectum and bowel), such that the dose that can be safely delivered to the prostate by EBRT is of the order of 64 Gy in 2 Gy per day fractions. Several technological advances over the last 20 years have enhanced the precision of EBRT, and have resulted in improved outcomes.
- The 3D-CRT approach reduces the dose-limiting late side-effect of proctitis [Dearnaley DP, *et al* 1999] and has allowed for dose escalation to the whole prostate to up to78 Gy.

Intensity Modulated Radiotherapy (IMRT)

- IMRT is an advanced technique which has superseded 3D-CRT. IMRT can modify the shape and intensity of the multiple radiotherapy beams. It is very precise in targeting the treatment area, sparing surrounding tissue and allowing dose escalation above 80 Gy. IMRT is currently recommended, particularly for the irradiation of pelvic lymph nodes.

Dose escalation

- Evidence suggests that patients treated with radiotherapy to the prostate have a significantly better outcome, because the dose to the gland is increased. The benefit is greatest in those patients with high-risk features.
- Debate remains over the best way of increasing the dose without significantly increasing normal tissue toxicity. 3D-CRT, IMRT and High Dose Rate (HDR) brachytherapy boost are methods currently under evaluation.
- Several randomised studies have shown that dose escalation with 3D-CRT and more recently with IMRT has a significant impact on the 5-year biochemical relapse free survival. However no trials to date have shown an improvement in long term overall survival.

- Evidence of the benefits of dose escalation has been demonstrated for T1–T3 prostate cancer by Pollack *et al*. in a phase III randomised study undertaken at the MD Anderson Hospital [Pollack A, *et al* 2002].
    - A total of 305 men were randomised between 1993 and 1998 to compare the efficacy of 70 Gy versus 78 Gy with a median follow-up of 60 months. The primary endpoint was freedom from failure (FFF), including biochemical failure, which was defined as three rises in PSA level.
    - The FFF rates for the 70 Gy and 78 Gy arms at 6 years were 64% and 70%, respectively (p=0.03). Dose escalation to 78 Gy preferentially benefited those with a pre-treatment PSA concentration >10 ng/ml; the FFF rate was 62% for the 78 Gy arm versus 43% for those who received 70 Gy (p=0.01). For patients with a pre-treatment PSA concentration ≤10 ng/ml, no significant dose-response relationship was found, with an average 6-year FFF rate of about 75%.
    - Although no difference in OS occurred, the freedom from distant metastasis rate was higher for those with PSA levels >10 ng/ml who were treated to 78 Gy (98% versus 88% at 6 years, p=0.056).
- Dearnaley and colleagues have reported their findings from the MRC RT01 study [Dearnaley DP, *et al* 2007].
    - In this 3D-CRT trial, 843 men were randomised to a standard dose of 64 Gy compared with an escalated dose of 74 Gy, with all men also receiving neoadjuvant hormone therapy.
    - Patients receiving the conventional dose had 5-year biochemical PFS rates of 60% compared to 71% in the dose-escalated arm. Advantages were also seen in terms of clinical PFS and the decreased use of androgen suppression.
    - An update of this study with 10 years of follow up has not shown an a further benefit in biochemical PFS of 54% (172 events) versus 42% (224 events) , HR 0.688 (0.56-0.84) p<0.0001 in favour of the dose escalated group. However, no overall survival benefit was demonstrated, with both the 64 Gy and 74 Gy arms having an overall survival of 70% HR 0.99 (0.77-1.28) p=0.337. The number of men requiring long term hormone therapy was reduced in the dose escalated arm HR 0.77 (0.59-1.00) p=0.05 [Dearnaley DP, *et al* 2011].
- Recently the long-term follow-up of the pilot study, which provided the initial safety and feasibility information for the national MRC RT01 trial have been published [Creak A, *et al* 2013].
    - In this study, 126 patients were randomised to a standard dose of 64 Gy compared with an escalated dose of 74 Gy after neoadjuvant androgen suppression.
    - After a follow up of 13.7 years, 49 of 126 patients restarted AS, 34 developed metastases and 28 developed CRPC. Median OS was 14.4 years.
- Although escalated dose results were favourable, no statistically significant differences were seen between the randomised groups; PSA control (hazard ratio (HR): 0.77 (95% confidence interval (CI): 0.47–1.26)), development of CRPC (HR: 0.81 (95% CI: 0.40–1.65)), PC-specific survival (HR: 0.59 (95% CI:0.23–1.49)) and OS (HR: 0.81 (95% CI: 0.47–1.40))
- The Dutch randomised phase III trial comparing 68 Gy with 78 Gy also demonstrated a significant increase in the 5-year rate of freedom from clinical or biochemical failure in patients treated with a higher dose of radiotherapy [Peeters ST, *et al* 2006].

- The phase III trial of the French Federation of Cancer Centres compared 70 Gy with 80 Gy in men with localised prostate cancer, in 306 patients with a low risk of pelvic lymph node involvement [Beckendorf V, *et al* 2011]. At a median follow up of 61 months, they demonstrated improved 5-year biological outcomes in favour of dose-escalated radiotherapy group. Using the Phoenix definition, the 5-year biochemical relapse rate was 32% and 23.5%, respectively (p = .09).
- Although these and other studies have shown benefits from dose escalation this has been offset to a degree by a reported increase in late rectal toxicity.
- Prospective non-randomised studies conducted at the Memorial Sloan Kettering cancer centre have compared the outcomes of 1100 men who received doses in the range of 64–70 Gy and 76–86 Gy using IMRT [Zelefsky MJ, *et al* 2001].
    - The results were evaluated within prognostic risk groups (using clinical stage, Gleason grade and presenting PSA concentration). They demonstrated that increasing the dose delivered beyond 70.2 Gy in men with intermediate- and high-risk disease improved the 5-year actuarial PSA relapse-free survival rate from 50% to 70% and 21% to 47%, respectively, in these two risk categories.
- IMRT has the potential to reduce late rectal toxicity as shown in a further study that reports 3-year actuarial ≥grade 2 gastrointestinal toxicity at 4% [Zelefsky MJ, *et al* 2002].
- A further development under investigation involves a change in the traditional fractionation schedules. Hypofractionation may improve cancer control for the same level of radiation-related toxicity and be a more effective treatment for prostate cancer with a predicted low alpha/beta ratio. Phase II dose escalation studies using shortened schedules of hypofractionated IMRT regimens have indicated acceptable early toxicity [Zelefsky MJ, *et al* 2001].
- The CHHiP (Conventional or Hypofractionated High Dose IMRT for Prostate Cancer) study is currently recruiting patients in the UK to compare standard fractionation IMRT (74 Gy in 37 fractions) to two hypofractionated IMRT regimens (60 Gy in 20 fractions or 57 Gy in 19 fractions) in combination with neoadjuvant hormone therapy [Zelefsky MJ, *et al* 2002]. There is no overall survival data available from this trial as yet but preliminary safety results have shown that hypofractionated high-dose radiotherapy seems equally well tolerated as conventionally fractionated treatment at 2 years
- Debate remains over the best way of increasing the dose without significantly increasing normal tissue toxicity. 3D-CRT, IMRT and HDR brachytherapy boost are methods currently under evaluation.

Image Guided Radiotherapy (IGRT)

The advantages of dose escalation using IMRT means that organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity to the bladder, rectum and bowel. Techniques should therefore combine IMRT with some form of IGRT (fiducial markers, imaging), in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still under investigation.

Radiotherapy target volume/lymph nodes

- In high-risk patients the consensus is that the seminal vesicles should be included. There remains some debate for the benefit for prophylactic whole-pelvic irradiation, since randomised trials have failed to show conclusive advantages.
- The RTOG 9413 trial was designed to determine whether there was an advantage in terms of PFS with androgen deprivation therapy, whole pelvic radiotherapy followed by a prostate boost compared with androgen deprivation therapy and prostate-only radiotherapy. The trial also investigated the timing of hormone therapy with a further randomisation. One group received neoadjuvant hormone therapy followed by concurrent total androgen suppression and radiotherapy while the other group was treated with radiotherapy followed by adjuvant hormone therapy. Patients with non-metastatic disease but an estimated risk of lymph node involvement of >15% were randomised between the 4 arms [Lawton CA, *et al* 2007].
    - The difference in OS for the 4 arms was statistically significant (p=0.027).
    - However, no statistically significant differences were found in PFS or OS between neoadjuvant versus adjuvant hormone therapy and whole pelvis radiotherapy compared with prostate-only radiotherapy. A trend towards a difference was found in PFS (p=0.065) in favour of the whole pelvic radiotherapy + neoadjuvant hormone arm compared with the prostate-only radiotherapy + neoadjuvant hormones and whole pelvic radiotherapy + adjuvant hormone treatment arms.
    - These results have demonstrated that when neoadjuvant hormone therapy is used in conjunction with radiotherapy, whole pelvic treatment yields a better PFS than prostate-only radiotherapy. It also showed an improved OS when whole pelvic radiotherapy was combined with neoadjuvant rather than short-term adjuvant hormone therapy.

Patient selection

- EBRT can be unsuitable for patients with bilateral hip replacement, previous radiotherapy, severe proctitis or bowel morbidity.

Side-effects

- Acute complications include cystitis, faecal frequency and urgency, proctitis and rectal bleeding.
- Late complications occurring 3 months or later after treatment include impotence, bleeding, proctitis and diarrhoea.

HDR brachytherapy boost

- HDR brachytherapy using an iridium-92 temporary implant is a safe, reproducible and effective way of boosting conventional EBRT. There is published evidence for this approach demonstrating improved biochemical control and cause-specific survival without a significant increase in toxicity.
- Currently, HDR brachytherapy is mainly used as a boost treatment in combination with EBRT
- In a single randomised trial of EBRT vs. EBRT plus HDR brachytherapy boost, 220 patients with organ confined prostate cancer were randomised to EBRT alone with a dose of 55 Gy in 20 fractions, or EBRT with a dose of 35.75 Gy in 13 fractions, followed by HDR brachytherapy with a dose of 17 Gy in two fractions over 24 hours. In comparison with EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in the biochemical relapse free survival (P = 0.03). There were no differences in the rates of late toxicity. Patients randomly assigned to EBRT plus brachytherapy had a significantly better QoL as measured by their Functional Assessment of Cancer Therapy-Prostate (FACT-P) score at 12 weeks. However, a very high, uncommon rate of early recurrences was observed in the EBRT arm alone, even after 2 years, possibly due to the uncommon fractionation used [Hoskin PJ, *et al* 2007].

- A further single centre study evaluated the 10-year outcomes for 472 intermediate- and high-risk prostate cancer patients treated with pelvic EBRT to a dose of 46 Gy in 23 fractions and a HDR brachytherapy boost. The HDR dose fractionation was divided into two dose levels. The prostate biologically equivalent dose (BED) low-dose-level group received <268 Gy, and the high-dose group received >268 Gy. Phoenix biochemical failure (BF) definition was used.At a median follow up of 8.2 years , the 10-year biochemical failure rate 43.1% vs. 18.9%, ($p < 0.001$), the clinical failure rate of 23.4% vs. 7.7%, ($p < 0.001$), and the distant metastasis of 12.4% vs. 5.7%, ($p = 0.028$) were all significantly better for the high-dose level group. Grade 3 genitourinary complications were 2% and 3%, respectively, and grade 3 gastrointestinal complication was <0.5%.This prospective trial using P-EBRT with HDR boost and hypofractionated dose escalation demonstrates a strong dose-response relationship for intermediate- and high-risk prostate cancer patients [Martinez AA, *et al* 2011].

EBRT plus neoadjuvant hormone therapy

- Neoadjuvant hormone therapy reduces prostate volume by 30–40% [Shearer RJ, *et al* 1992; Forman JD, *et al* 1995]. This can reduce the size of the treatment field and as a result the potential level of toxicity experienced.
- There are also reports of an additive or synergistic effect on tumour cell kill with combined therapy. Theories as to the mechanism of this include improved oxygenation by reducing tumour bulk and movement of hormone-responsive cells into a resting phase, which could reduce repopulation rate and enhance tumour cell death (increased apoptosis) [Hara I, *et al* 2002].
- The RTOG 86-10 trial randomised 471 men with T2–T4 prostate cancer to radiotherapy +/– 4 months of ADT (goserelin 3.6 mg depot once-monthly plus flutamide 250 mg tid) before and during EBRT or to radiotherapy alone. The median follow-up was 6.7 years for all patients and 8.6 years for surviving patients [Pilepich MV, *et al* 2001].
    - At median follow-up of 8.7 years for surviving patients, there was a trend to improved survival (8-year survival 53% versus 44%, p=0.1) for those treated by hormone therapy with radiotherapy, which was significant for the subgroup with Gleason grade 2–6 disease (70% versus 52%, p=0.015) [Pilepich MV, *et al* 2001].
    - Ten-year OS estimates (43% versus 34%) and median survival times (8.7 versus 7.3 years) favoured combined therapy with hormones and radiation compared to radiation treatment alone; however, these differences did not reach statistical significance (p=0.12) [Roach M, *et al* 2008].
    - There was a statistically significant improvement in 10-year disease-specific mortality (23% versus 36%; p=0.01), distant metastases (35% versus 47%; p=0.006), DFS (11% versus 3%; p<0.0001) and biochemical failure (65% versus 80%; p<0.0001) with the addition of neoadjuvant hormone therapy, but no differences were observed in the risk of fatal cardiac events [Roach M, *et al* 2008].

EBRT plus adjuvant hormonal therapy

- Long-term application of adjuvant androgen suppression should be seriously considered in prostate cancer patients with an unfavourable prognosis.
- A combination of radiotherapy and hormone therapy is superior to radiotherapy alone in patients with locally advanced disease. The combination is associated with better survival and increased time to progression.
- Optimal duration of adjuvant therapy is uncertain (6 months to indefinite) and the results of further studies are awaited.

Clinical evidence

- Adjuvant androgen suppression immediately after radical radiotherapy has been shown to significantly increase OS, PFS, and significantly reduce local progression, distant metastases and biochemical progression in several large randomised studies.
- Bolla *et al*. (EORTC 22863) randomised 415 patients with locally advanced prostate cancer (T1–4, Nx, M0) to receive either radiotherapy with immediate goserelin 3.6 mg therapy (every 4 weeks for 3 years) plus cyproterone acetate (CPA) during the first month of treatment for disease flare (n=207) or radiotherapy alone (n=208) [Bolla M, *et al* 2010].
    - After a mean follow-up of 9.1 years the 10-year clinical DFS was 22·7% (95% CI 16·3-29·7) in the radiotherapy-alone group and 47·7% (39·0-56·0) in the combined modality therapy group (HR= 0·42, 95% CI 0·33-0·55, p<0·0001). The 10-year OS was 39·8% (95% CI 31·9-47·5) in patients receiving radiotherapy alone and 58·1% (49·2-66·0) in those allocated combined treatment (HR 0·60, 95% CI 0·45-0·80, p=0·0004), and 10-year prostate-cancer mortality was 30·4% (95% CI 23·2-37·5) and 10·3% (5·1-15·4), respectively (HR 0·38, 95% CI 0·24-0·60, p<0·0001). No significant difference in cardiovascular mortality was noted between treatment groups.
- In the EORTC 22961 study, men with locally advanced prostate cancer who had all previously completed EBRT and 6 months of adjuvant ADT were randomised to receive either no further treatment (short-term ADT), or 2.5 years of further treatment with a LHRH agonist (long-term ADT) [Bolla M, *et al* 2009].
    - The 5-year overall mortality rates were 19.0% for short-term ADT versus 15.2% for long-term ADT (HR 1.42; p=0.65 for non-inferiority).
    - The 5-year prostate cancer-specific mortality rates were 4.7% for short-term ADT versus 3.2% for long-term ADT (HR 1.71; 95%CI: 1.14–2.57; p=0.002).
    - This study showed inferior survival for men treated with RT and 6 months of ADT compared with RT plus 3 years of ADT in the treatment of locally advanced prostate cancer.
- Pilepich *et al*. (RTOG 85-31) randomised 977 patients with locally advanced non-metastatic prostate cancer to receive either pelvic radiation plus goserelin 3.6 mg depot (started during the last week of radiotherapy, to be continued indefinitely every month or until relapse; n=488) or radiotherapy alone (n=489) [Pilepich MV, *et al* 2005].
    - A total of 945 patients remained appropriate for analysis: 477 in the adjuvant arm and 468 in the control arm. Thirty-two patients were retrospectively classified as ineligible. the most common reason was a T2 primary tumour with negative lymph nodes
    - Median follow-up was 7.6 years for all patients and 11 years for surviving patients.
    - The data clearly identified that the use of goserelin in combination with radiotherapy in this group of high-risk patients resulted in significant improvements in all endpoints.
    - Goserelin adjuvant therapy significantly (p<0.002) reduced the risk of dying by approximately 25%. The absolute 10-year survival rate compared with radiotherapy alone was 49% versus 39%. The improvement in survival appeared preferentially in patients with a Gleason grade of 7–10.
    - Goserelin treatment also resulted in a significant improvement in local control, freedom from distant metastasis, DFS and biochemical DFS.

- Horwitz *et al*. (RTOG 92-02) investigated the use of long-term androgen suppression following neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced prostate cancer (T2c to T4 with no extra pelvic lymph node involvement and PSA <150 ng/ml) [Horwitz EM, *et al* 2008].
    - A total of 1554 patients were treated with goserelin and flutamide for 2 months prior to and 2 months during radiotherapy, and then randomised to 24 months of goserelin long-term (LTAD) or no further treatment short-term hormone therapy (STAD).
    - At 10 years, the LTAD and radiotherapy group showed significant improvement over the STAD + radiotherapy group for all endpoints except OS: DFS (13.2% versus 22.5%; p<0.0001), disease-specific survival (83.9% versus 88.7%; p=0.0042), local progression (22.2% versus 12.3%; p<0.0001), distant metastasis (22.8% versus 14.8%; p<0.0001), biochemical failure (68.1% versus 51.9%; p≤0.0001) and OS (51.6% versus 53.9%, p=0.36).
    - One subgroup analysed consisted of all cancers with a Gleason score of 8–10 cancers. An OS difference was observed (31.9% versus 45.1%; p= 0.0061), as well as in all other endpoints.
- As previously described, in the EPC study, exploratory analyses were conducted to determine the efficacy of bicalutamide in clinically relevant subgroups with a median follow-up of 9.7 years at the third analysis. The primary endpoints were objective PFS and OS [McLeod DG, *et al* 2006].
- Patients who derived benefit from bicalutamide in terms of PFS were those with locally advanced disease, with OS significantly favouring bicalutamide in patients with locally advanced disease undergoing radiotherapy (HR = 0.70 (CI 0.51 to 0.97), p=0.03). The overall tolerability of bicalutamide was consistent with previous analyses, with breast pain (73.7%) and gynaecomastia (68.8%) the most frequently reported adverse events in patients randomized to bicalutamide.

Radical Prostatectomy

There is debate about the role of radical prostatectomy for men with locally advanced or high risk prostate cancer. Surgical treatment of this stage has traditionally been discouraged because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse

Radical prostatectomy may be considered for selected cases with low volume tumour provided that the tumour is not fixed to the pelvic side wall, or that there is no invasion of the urethral sphincter. Management decisions should be made after all treatments have been discussed by the multidisciplinary team and after the balance of benefits and side effects of each therapy modality have been considered by the patients with regard to their own individual circumstances. It is essential that patients are counselled regarding the high risks of needing additional adjuvant and salvage therapies and understand that the surgery may be part of a multimodality approach.

It is recommended that lymph node dissection should be performed in all high-risk cases.

Clinical evidence

- The Mayo clinic have reported 15-year outcomes for 5662 men with locally advanced prostate cancer treated with radical prostatectomy [Ward JF, *et al* 2005].
    - Freedom from local or systemic disease at 5, 10, and 15 years after radical prostatectomy were reported as 85%, 73% and 67%; the respective cancer-specific survival rates were 95%, 90% and 79%. Significantly many men who did not receive neoadjuvant therapy (27%) were clinically over-staged (pT2) and most men with pT3 disease (78%) received adjuvant therapy. The mean time to adjuvant therapy after radical prostatectomy was 4.0 years. Pathological grade (> or =7), positive surgical margins, and nondiploid chromatin were all independently associated with a significant risk for clinical disease recurrence, while preoperative PSA level had little effect on outcome.
    - The authors also noted that many patients with clinically T3 prostate cancer are overstaged (pT2) (27% in this series who did not have neoadjuvant hormone therapy)
- In a further single institution series the 10-year outcomes of radical prostatectomy in 200 men with unilateral clinical T3a disease who had not received neoadjuvant hormone therapy, have been reported by Hsu [Hsu CY, *et al* 2007]. Clinical over-staging was again noted in 23.5% of cases who had a pathological stage of pT2. 56% of patients received adjuvant or salvage therapy. The overall survival at 5 and 10 years was 95.9% and 77.0%, respectively, and cancer specific survival was 98.7% and 91.6%. Biochemical progression free survival (BPFS) at 5 and 10 years was 59.5% and 51.1%, respectively, and clinical progression free survival (CPFS) was 95.9% and 85.4%. Margin status was a significant independent predictor in BPFS; cancer volume was a significant independent predictor in CPFS.

Radical Prostatectomy and Neoadjuvant/Adjuvant Hormone Therapy

- A review and meta-analysis of the role of NHT and prostatectomy has shown that NHT before prostatectomy did not improve OS or disease-free survival (DFS), but did significantly reduce positive margin rates [relative risk (RR): 0.49; 95% confidence interval (CI): 0.42-0.56, P < 0.00001), organ confinement (RR: 1.63; 95% CI: 1.37-1.95, P < 0.0001) and lymph node invasion (RR: 0.49; 95% CI: 0.42-0.56, P < 0.02) [Shelley MD, *et al* 2009]. Therefore, evidence suggests that the down-staging achieved with neoadjuvant hormone therapy does not translate into improved DFS, and therefore cannot be recommended outside of clinical trials [Bonney WW, *et al* 1999; Paul R, *et al* 2004; Selli C & Milesi C. 2004; Witjes WPJ, *et al* 1997].

- Similarly, there is currently no evidence that adjuvant hormone therapy provides a survival advantage for patients with pathologically proven localised disease [Hachiya T, *et al* 2002; Prayer-Galetti T, *et al* 2000]. A recent Cochrane review and metaanalysis studied the role of adjuvant HT following RP: the pooled data for 5-year OS demonstrated an odds ratio (OR) of 1.50 and 95% CI: 0.79-2.84 [Shelley MD, *et al* 2009]. Although this finding was not statistically significant, there was a trend favouring adjuvant HT. There was no survival advantage at 10 years. The pooled data for DFS gave an overall OR of 3.73 and 95% CI: 2.3-6.03. The overall effect estimate was highly significant (P < 0.00001) in favour of the HT arm.
- The ECOG 7887 trial compared adjuvant ADT after radical prostatectomy and deferred hormonal therapy in patients with nodal metastases [Messing EM, *et al* 2006]. A total of 98 patients with locally advanced prostate cancer (T1–T2, N+ disease) who had undergone pelvic lymphadenectomy were included in the study. These patients were randomised to receive adjuvant hormone ablation or followed until disease progression and then given hormone therapy [Messing EM, *et al* 2006].
    - At 11.9 years' median follow-up, adjuvant ADT increased survival by 2.6 years compared with surgery alone, in node-positive patients. Median survival in the adjuvant ADT and deferred treatment groups was 13.9 and 11.3 years, respectively. 64% of patients treated with adjuvant ADT were still alive at this time, compared with 45% of patients who received radical prostatectomy alone.
    - In this setting, adjuvant ADT reduced the risk of dying by approximately 46% compared with RP alone (HR 0.54; 95%CI: 0.99–0.30; p=0.04).

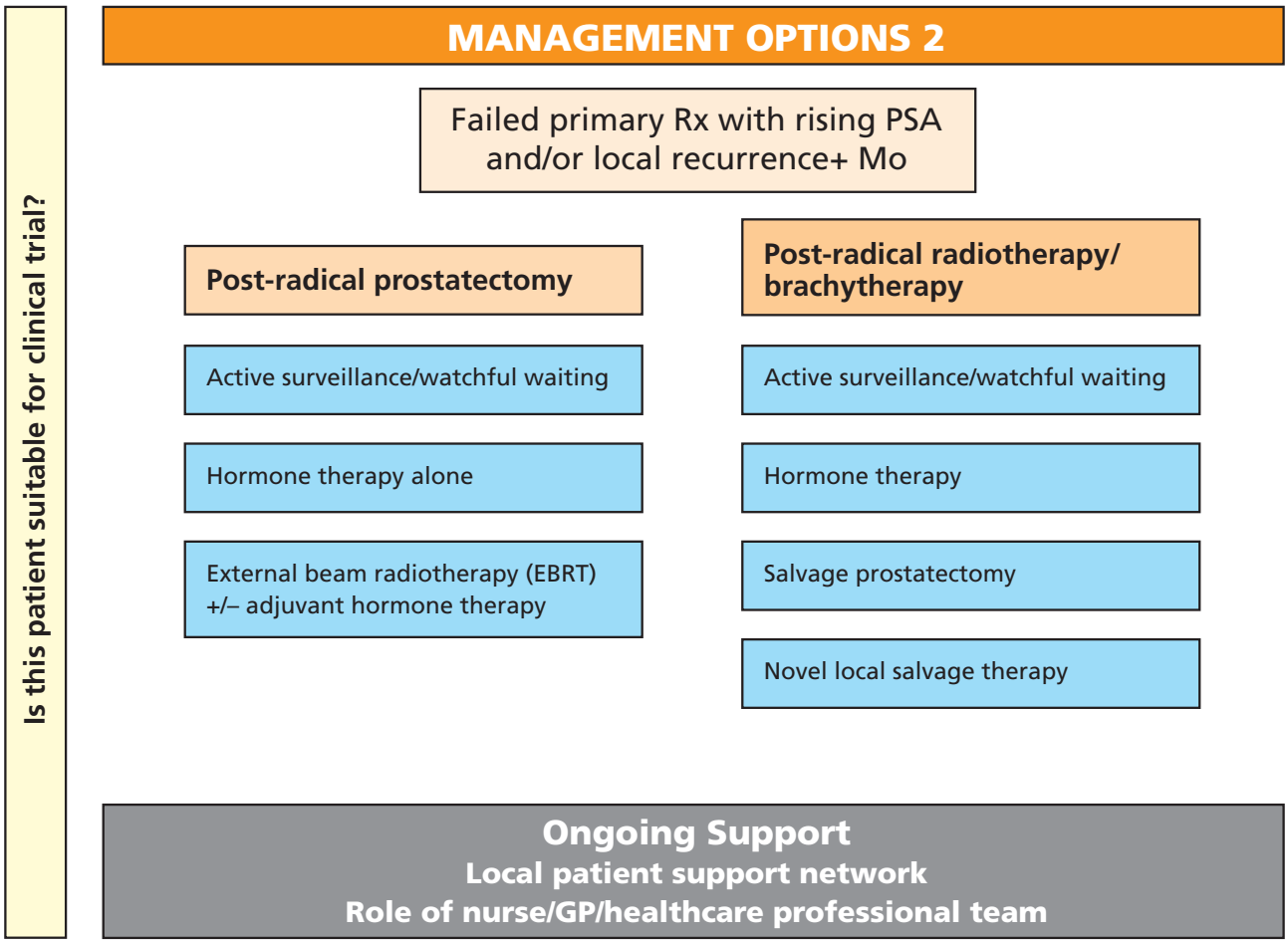
Radical Prostatectomy and Adjuvant Radiotherapy

- Extracapsular invasion (pT3), Gleason score > 7, and positive surgical margins (R1) can be associated with a risk of local recurrence [Hanks GE. E 1988]. Adjuvant radiotherapy has been assessed in three prospective randomised studies
- The EORTC 22911 study was designed to investigate benefit for immediate postoperative radiotherapy (60 Gy) in a target sample size of 1005 patients with pT3 disease or positive surgical margins as opposed to salvage radiotherapy offered for biochemical or clinical relapse [Bolla M, *et al* 2012].
    - After a median follow up of 10 years, overall survival did not differ significantly between the treatment arms. For patients younger than 70, the study concluded that adjuvant RT significantly improved the 10-year biological PFS: 60.6% vs. 41.1%. A previous reported difference in the clinical progression rates for the entire cohort that favoured adjuvant RT after 5 years of follow up was not sustained at 10 years, although locoregional control was improved after immediate irradiation (hazard ratio, HR = 0.45, P < 0.0001).
    - In terms of toxicity, adjuvant RT was well tolerated with no reported Grade 4 toxicity. The grade 3 genitourinary toxicity rate was 5.3%, in comparison with 2.5% in the observation group after 10 years.
- SWOG 8794 reported the results of 425 men with pT3 disease who were randomised to adjuvant radiotherapy to the prostate bed (60–64 Gy) or observation and subsequent salvage therapy [Swanson GP, *et al* 2008]. At a median follow up of more than 12 years, this study demonstrated a significant improvement in metastasis-free survival, with a 10-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, P = 0.016) and a 10-year OS of 74% vs. 66% (median: 1.9 years prolongation; P = 0.023)

- The ARO trial 96-02 randomly assigned men with pT3 N0 tumours and an undetectable post operative PSA to immediate post operative radiotherapy (114 men) or a 'wait and see' policy (154 men). After a median follow-up period of 54 months, the radiotherapy group demonstrated a significant improvement in biochemical PFS of 72% vs. 54%, respectively (P = 0.0015). Further follow up is needed to assess metastases-free survival and overall survival. The rate of grade 3 to 4 late adverse effects was 0.3% [Wiegel T, *et al* 2009].
- The Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) study is investigating the timing of radiotherapy (immediate versus early salvage) and hormone duration and will be important in guiding future decision making.

Locally Advanced Disease: Recurrence after Primary Treatment

Figure 3a: Treatment algorithm for locally advanced disease (cont.)



Rising PSA levels

- The PSA concentration at which to define treatment failure after prostatectomy varies in the literature. An international consensus states that recurrent cancer may be defined by two consecutive PSA values of > 0.2 ng/mL [Heidenreich A, *et al*. EAU guidelines 2013].

Definitions of recurrence

- The Phoenix definition of relapse after radiotherapy is PSA nadir plus 2 ng/ml [Roach M, *et al* 2006].
- Patients whose PSA never falls to an undetectable level in the post-operative period are generally considered to have systemic disease. However, some may have local disease amenable to salvage radiotherapy, and so need to be carefully assessed to determine the best management plan.
- A PSA concentration that rises rapidly in the post-operative setting may be indicative of metastatic disease, while a PSA that remains undetectable over a long period then gradually rises may be more likely to indicate local recurrence.

- Pound *et al*. carried out a retrospective review of 1997 men undergoing radical prostatectomy by a single surgeon for clinically localised disease with no neoadjuvant or adjuvant treatment [Pound CR, *et al* 1999]. A PSA ≥0.2 ng/ml was deemed evidence of recurrence.
    - At 15 years, 15% had PSA elevation and 34% of these had developed metastases.
    - The median time from PSA elevation to metastatic disease was 8 years.
    - After development of metastases, the median actuarial time to death was 5 years. In the survival analysis, time to biochemical progression, Gleason grade and PSA doubling time were predictive of the probability and time to the development of metastatic disease.
- After completion of radiotherapy and hormonal treatment, testosterone recovery usually occurs. This may cause some PSA elevation that is related to normal prostate tissue recovery and not disease recurrence.
- The definition of disease recurrence in the setting of combined therapy remains a matter of debate and consensus is awaited.
- Benign PSA rises (PSA bounce) occur in approximately 12% of patients following EBRT and 30% following LDR brachytherapy in the absence of neoadjuvant hormonal treatment (starting between 18 months and 2 years after treatment).

Local recurrence after radical prostatectomy

Overview

- Overall, approximately 40% of patients who have a radical prostatectomy have biochemical evidence of recurrence at some point.
- Determining whether relapse is local or distant is important in determining optimal treatment. However, post-prostatectomy imaging is often unhelpful. Other factors that may aid this distinction include:
  - Timing and pattern of PSA relapse (rapid rise post-operatively favours distant spread)
  - Involvement of seminal vesicles or lymph nodes
  - Margin status at surgery
  - Gleason grade
- Radical salvage treatment is usually via radiotherapy to the prostate bed +/– hormone therapy. The optimal time of treatment, i.e. immediate adjuvant or early salvage EBRT, is currently uncertain. The timing and duration of hormone therapy is also unclear.
- The RADICALS study is investigating the timing of radiotherapy (immediate versus early salvage) and hormone duration [Parker C, *et al* 2007].

Clinical evidence

- Extracapsular invasion (pT3), Gleason score > 7, and positive surgical margins (R1) can be associated with a risk of local recurrence [Hanks GE. 1988]. Adjuvant radiotherapy has been assessed in three prospective randomised studies.

Adjuvant radiotherapy

- The EORTC 22911 study was designed to investigate benefit for immediate postoperative radiotherapy (60Gy) in a target sample size of 1005 patients with pT3 disease or positive surgical margins as opposed to salvage radiotherapy offered for biochemical or clinical relapse [Bolla M, *et al* 2012].

  After a median follow up of 10 years, overall survival did not differ significantly between the treatment arms. For patients younger than 70, the study concluded that adjuvant RT significantly improved the 10-year biological PFS: 60.6% vs. 41.1%. A previous reported difference in the clinical progression rates for the entire cohort that favoured adjuvant RT after 5 years of follow up was not sustained at 10 years, although locoregional control was improved after immediate irradiation (hazard ratio, HR = 0.45, P < 0.0001).

  In terms of toxicity, adjuvant RT was well tolerated with no reported Grade 4 toxicity. The grade 3 genitourinary toxicity rate was 5.3%, in comparison with 2.5% in the observation group after 10 years.

- SWOG 8794 reported the results of 425 men with pT3 disease who were randomised to adjuvant radiotherapy to the prostate bed (60–64 Gy) or observation and subsequent salvage therapy [Swanson GP, *et al* 2008]. At a median follow up of more than 12 years, this study demonstrated a significant improvement in metastasis-free survival, with a 10-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, P = 0.016) and a 10-year OS of 74% vs. 66% (median: 1.9 years prolongation; P = 0.023)

- The ARO trial 96-02 randomly assigned men with pT3 N0 tumours and an undetectable post-operative PSA to immediate post operative radiotherapy (114 men) or a 'wait and see' policy (154 men). After a median follow-up period of 54 months, the radiotherapy group demonstrated a significant improvement in biochemical PFS of 72% vs. 54%, respectively (P = 0.0015). Further follow up is needed to assess metastases-free survival and overall survival. The rate of grade 3 to 4 late adverse effects was 0.3% [Wiegel T, *et al* 2009].

- Further results are awaited from a recently completed randomised controlled phase III study from the RTOG-96-01 in 771 men comparing salvage radiotherapy and placebo vs. a combination of salvage radiotherapy and bicalutamide 150 mg daily in the postoperative setting [Heney N *et al*, 2010]. At a median follow-up of 7.1 years, actuarial OS at 7 years was 91% for the RT and bicalutamide group and 86% for RT alone. Too few primary end-point events have occurred to allow a statistical comparison between groups. Freedom from PSA progression at 7 years was 57% for the combined modality group and 40% for RT alone (P < 0.0001) and for the 134 men with Gleason Score 8-10 was 56% and 26% (P < 0.0008). The 7-yr cumulative incidence of metastatic prostate cancer was less in the RT and bicalutamide arm, 7% vs. 13% in the RT alone arm (p<0.041). Late grade 3-4 toxicities were similar in both arms.

- The Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) study is investigating the timing of radiotherapy to a dose of 66Gy in 33 fractions (immediate versus early salvage) and hormone duration and will be important in guiding future decision making.

Salvage hormone therapy

- Systemic failure following radical prostatectomy is predicted with > 80% accuracy by a PSA relapse < 1 year, a PSADT of 4-6 months, Gleason score 8-10, and stage pT3b, pTx pN1. In this situation early hormone therapy may help delay progression in selected patients.
- A retrospective study including 1,352 patients with postoperative PSA recurrence showed no significant difference overall in the time to clinical metastases with early hormone therapy (after PSA recurrence, but before clinical metastases) vs. delayed hormone therapy (at the time of clinical metastases). However, for high risk patients (Gleason score > 7 and/or a PSA doubling time < 12 months) it was found that early hormone therapy delayed the time to clinical metastases although had no overall impact on prostate cancer specific mortality [Moul JW, *et al* 2004].

Recurrence after radical radiotherapy

Overview

- After radiotherapy, local failure is documented by a positive prostatic biopsy and negative imaging studies for systemic disease such as CT or MRI and bone scan.
- It must however be noted that most imaging studies are not sensitive enough to identify the anatomic location of relapsing PCa at PSA levels < 0.5-1.0 ng/mL. Prostatic biopsy after RT is only considered necessary if local procedures with curative intent, such as a salvage radical prostatectomy, are indicated in an individual patient.
- The therapeutic options for recurrence following radiotherapy include:
    - Salvage radical prostatectomy: associated with 5-year biochemical DFS rates of 55–69%, but the technique is associated with a significant incidence of complications, such as rectal injury, anastamotic stricture and urinary incontinence. In general, salvage radical prostatectomy should be considered only after multidisciplinary team and patient discussion with regards to potential benefits and toxicities. It should be limited to men with low comorbidity, a life expectancy of at least 10 years, an organ-confined prostate cancer with a Gleason score < 7, and preoperative PSA < 10 ng/mL.
    - Salvage cryotherapy: 5-year biochemical PFS ranges from 40% to 73%. The complications of salvage cryotherapy are erectile dysfunction, pelvic, rectal or perineal pain, recto-urethral fistula, bladder outlet obstruction and urethral stricture.
    - Salvage HIFU is currently under investigation.
    - Hormone therapy can be given in combination with local treatments or as monotherapy.

Clinical evidence

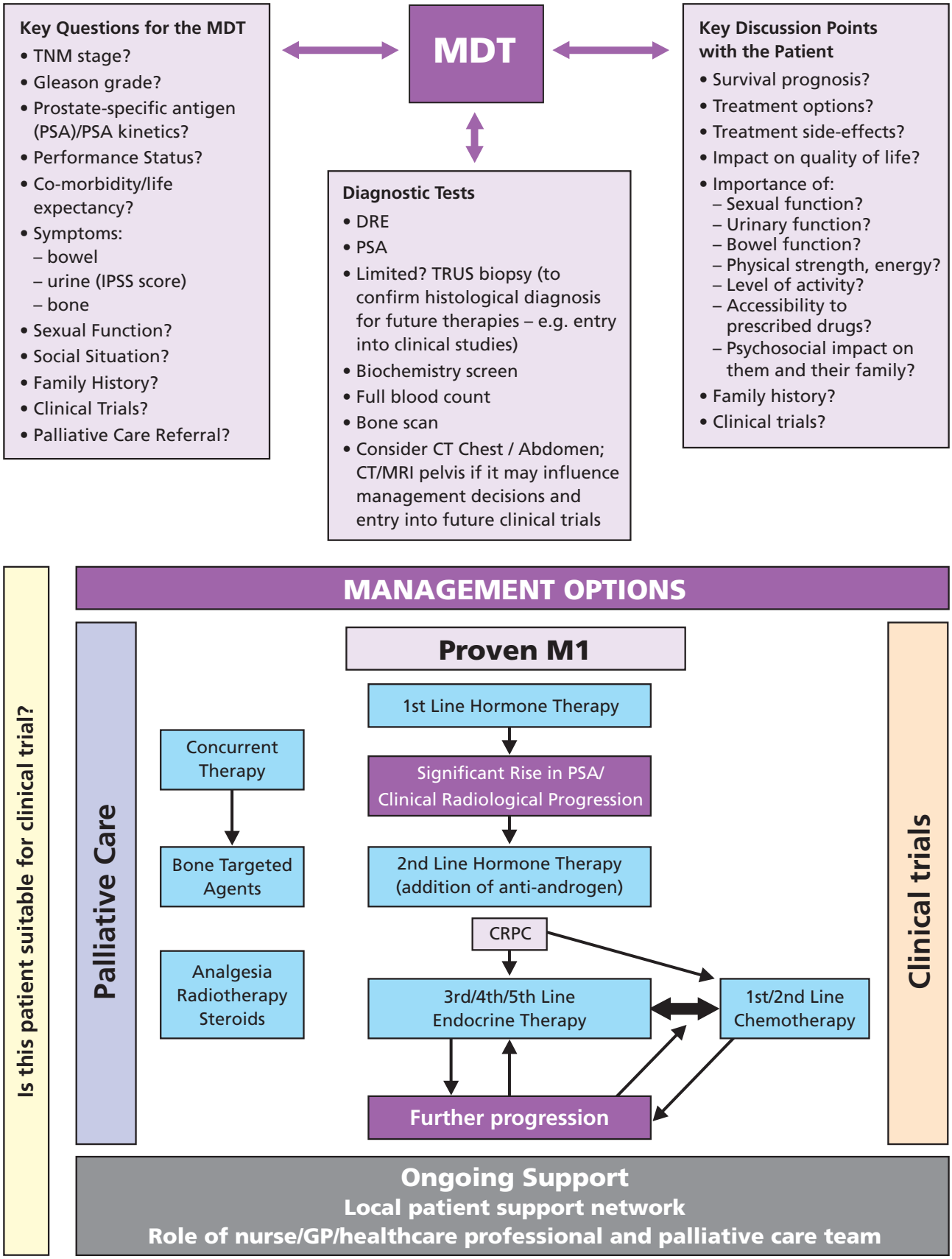
- In a recent systematic review of the literature, Chade *et al*. showed that salvage radical prostatectomy allowed 5-year and 10-year biochemical recurrence-free survival estimates ranging from 47% to 82% and from 28% to 53%, respectively. The 10-year cancer-specific and OS rates ranged from 70% to 83% and from 54 to 89%, respectively. The PSA value before salvage radical prostatectomy and prostate biopsy Gleason score were the strongest predictors of the presence of organ-confined disease, progression, and cancer specific survival [Chade DC, *et al* 2011]
- The four studies of salvage cryotherapy reviewed used varying definitions of recurrence. The 5-year biochemical PFS ranged from 40% when failure was defined as PSA 2 above nadir, to 62% and 73% when failure was defined as PSA greater than 2 and greater than 4, respectively.
    - The complications of salvage cryotherapy are erectile dysfunction, pelvic, rectal or perineal pain, rectourethral fistula, bladder outlet obstruction and urethral stricture.
- In a multicentre study reporting the current outcome of salvage cryotherapy in 279 patients, the 5-year biochemical -free survival estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15 of the 46 patients (32.6%) who underwent prostate biopsy following the procedure. The urinary incontinence rate was 4.4%. The rectal fistulae rate was 1.2%, and 3.2% of patients had to undergo transurethral resection of the prostate (TURP) for removal of sloughed tissue [Pisters LL, *et al* 2008].
- In 71 patients with localised disease following EBRT who were treated with salvage HIFU, 80% demonstrated negative biopsies and 61% had a nadir PSA concentration <0.5 ng/ml [Gelet A, *et al* 2004].
    - At a mean follow-up of 14.8 months, 44% of the patients had no evidence of disease progression.
    - Adverse events included recto-urethral fistula in 6%, grade 3 incontinence in 7%, and bladder neck stenosis in 17% of patients.

Salvage hormone therapy

- Patients with a PSA relapse who are not eligible for salvage therapy or who have high risk of systemic disease may be treated with immediate or delayed hormone therapy. Intermittent androgen deprivation for PSA elevation after radiotherapy may improve quality of life and theoretically delay hormone resistance. Overall survival rates of intermittent versus continuous androgen deprivation have been assessed in a noninferiority randomised trial.1386 patients with a PSA level greater than 3 ng/ml more than 1 year after primary or salvage radiotherapy for localised prostate cancer were randomised. Intermittent treatment was provided in 8-month cycles, with non-treatment periods determined according to the PSA level [Crook JM, *et al* 2012].
- At a median follow-up of 6.9 years, OS was 8.8 years in the intermittent-therapy group versus 9.1 years in the continuous-therapy group (hazard ratio for death, 1.02; 95% confidence interval, 0.86 to 1.21). The estimated 7-year cumulative rates of disease-related death were 18% and 15% in the two groups, respectively (P=0.24). Intermittent androgen deprivation was shown to be noninferior to continuous therapy in this setting with respect to OS. In the intermittent-therapy group, testosterone recovery to the trial-entry threshold occurred in 79%. Intermittent therapy provided potential benefits with respect to physical function, fatigue, urinary problems, hot flashes, libido, and erectile function.

Advanced (Metastatic) Prostate Cancer Management Options

Figure 4: Treatment algorithm for advanced (metastatic) disease



Based on MRC evidence, the majority of patients with advanced (metastatic) disease should be treated. Deferred treatment is acceptable only in highly selected, informed patients.

First line hormone therapy

Overview

- Androgen deprivation therapy (ADT) is standard first-line treatment for the management of patients with advanced disease. ADT can involve orchidectomy, LHRH agonists, and gonadotrophin-releasing hormone (GnRH) antagonists and anti-androgens
- Orchidectomy remains the gold-standard ADT against which all other treatments are compared because of its rapid effects on total testosterone concentrations [Tombal B.2007].
- The standard castrate level is <50 ng/dL. It was defined more than 40 years ago and current, more accurate methods of testosterone measurement have shown the mean value after surgical castration is 15 ng/dL(1.7 nmol/L) [Oefelein MG, *et al* 2000]. This has led to a revisiting of the current definition of castration, with many authors suggesting a more appropriate level is < 20 ng/dL
- Long-acting luteinising hormone-releasing hormone (LHRH) agonists have been used in advanced prostate cancer for more than 15 years. They are synthetic analogues of LHRH, generally delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. After the first injection, they stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH release leading to a testosterone and potential clinic flare phenomenon, which begins 2-3 days after administration and lasts for about 1 week. The effects of the testosterone flare can be blocked by the co administration of an antiandrogen before and up to 2 weeks after the initial injection. Survival is generally considered equivalent with LHRH agonists and orchidectomy [Vogelzang NJ, *et al* 1995; Kaisary AV, *et al* 1995]. Although a meta-analysis has indicated that 2-year survival may be worse with medical treatment than with orchidectomy [Seidenfeld J, *et al* 2000].
- Patients, however, generally prefer medical treatment and in terms of usage, drug treatment represents the standard of care for advanced prostate cancer [Shahinian VB, *et al* 2005; Shahinian VB, *et al* 2006; Cassileth BR, *et al* 1992].
- In contrast to LHRH agonists, GnRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a rapid decrease in LH, FSH and testosterone levels without any testosterone flare. Now licensed on the evidence of phase III clinical trial data, degarelix demonstrates reduced testosterone concentrations to below castrate levels in 3 days (90% decrease in median testosterone compared with leuprolide group experiencing a 65% increase in median testosterone levels; p<0.001) [Klotz L, *et al* 2010].
    - Degarelix shows long term suppression of testosterone for up to 364 days. 97.2% of patients on degarelix maintained medical castrate levels (<50 ng/dl from day 28 to Day 364 (95% /CIS) compared to 96.4% with leuprolide.
    - PSA levels were lowered by 64% after 2 weeks, 85% after 1 month and 95% after 3 months and remained suppressed throughout the 1-year treatment.
    - An extended follow-up has been recently published (median 27.5 months), suggesting that degarelix might result in better progression-free survival compared to monthly leuprorelin [Crawford ED, *et al* 2011].
    - Ongoing research suggests that degarelix may reduce the risk of further cardiovascular events in men who have suffered an event prior to commencing hormone therapy [Smith MR, *et al* 2011].
    - Degarelix can cause local skin reactions after delivery of the initial injection but this isles common with subsequent treatments.

Immediate versus deferred hormonal treatment

- All symptomatic advanced prostate cancer patients should have immediate treatment with ADT.
- Immediate versus deferred treatment for advanced prostate cancer was investigated by the MRC Prostate Working Party Investigators Group. An RCT of 943 men with asymptomatic metastases or locally advanced disease, not suitable for curative treatment, was undertaken, with randomisation to immediate or deferred hormone therapy [MRC Prostate Working Party Investigators Group 1997].
    - There was a significant advantage in the immediate treatment group in terms of distant progression. Mortality was only significantly changed by treating immediately in those with M0 disease (Table 6).
    - A modest but statistically significant increase in OS was seen in the immediate treatment group, but not significant difference in prostate cancer mortality or symptom-free survival was demonstrated.
    - Due consideration must therefore be given to potential effects of long-term ADT versus the potential avoidance of such effects in patients if hormone therapy is deferred [Studer UE, *et al* 2008].

Table 6: Effect of immediate versus deferred hormonal treatment [MRC Prostate Working Party Investigators Group 1997].

		Immediate	Deferred
Distant progression		26%	45%
Mortality due to prostate cancer	M0 disease M1 disease	31.6% No significant difference	48.8% No significant difference

Combined androgen blockade (CAB)

- There is debate over the use of combined androgen blockade (CAB). In 2000, the Prostate Cancer Trialists' Collaborative Group published a meta-analysis of the available trials of CAB versus monotherapy. The analysis included 27 trials, which incorporated 8275 men, representing 98% of men ever randomised in trials of CAB versus monotherapy [Prostate Cancer Trialists' Collaborative Group 2000; Klotz L 2001].
    - The 5-year survival for all patients receiving CAB was 25.4%, compared with 23.6% for patients receiving monotherapy.
    - In subgroup analyses, patients treated with cypretone acetate (CPA) seemed to fare slightly worse than those treated with flutamide or nilutamide, mostly secondary to non-prostate cancer-related deaths.

- If the CPA studies were excluded, the results were as follows [Prostate Cancer Trialists' Collaborative Group 2000]:
    - CAB with flutamide alone was associated with an 8% reduction in the risk of death (95%CI: 0.86–0.98; p=0.02), which translates to a small but significant improvement in 5-year survival over castration alone.
    - CAB with flutamide plus nilutamide was associated with an 8% reduction in the risk of death (95%CI: 1.00–1.27; p=0.005), which translates to a small but significant improvement in 5-year survival of 2.9% over castration alone.
    - Conversely, CAB with CPA is associated with an increased risk of death of 13% (95%CI: 1.00–1.27; p=0.04), which translates to a small but significant reduction in 5-year survival of 2.8% over castration alone.
- It can be concluded that the choice of anti-androgen used for CAB has an impact on outcome, and that CAB with a non-steroidal anti-androgen may offer a small but significant survival benefit.

Intermittent versus Continuous Androgen Blockade

- The use of intermittent androgen blockade (IAD) has the advantage of potentially reducing the toxicities of therapy and improving quality of life in the periods of no treatment and also a potential theoretical advantage of delaying the emergence of the androgen-independent clone.
- A systematic review has concluded that intermittent IAD was feasible and accepted by patients [Abrahamsson PA 2010]. Results from ongoing randomised controlled trials are awaited although many studies had mixed advanced and locally advanced patients and used different criteria for starting and stopping ADT and the duration of therapy time.
- A study of 766 patients conducted by the South European Uroncological (SEUG) Group included 30% with advanced disease. After a median follow-up of 51 months, there was no difference in either time to progression (HR: 0.81; p = 0.11) or overall survival (HR: 0.99). No overall quality of life benefit was demonstrated but there was a clear benefit for improved sexual function in the IAD group, with 28% sexually active vs. 10% in the continuous group at 15 months after randomization, respectively [Calais da Silva FE, *et al* 2009].
- The FinnProstate Study VII, randomized 554 patients (50% with advanced disease) to intermittent versus continuous ADT. After a median follow-up of 65 months, no significant difference was observed in the median PFS (34.5 months in the IAD group vs. 30.2 months in the continuous group, p = 0.29) in either the total study population or in the N+ or M1 subgroup populations. The median OS was 45 months in both groups.
- Results are awaited from the SWOG trial 9346, which is the largest study to randomize patients with advanced prostate cancer (1134 men out of 3040) to intermittent and continuous ADT [Hussain M, *et al* 2012]. The presented abstract indicated that IAD was not 'non inferior' compared to continuous ADT (median OS 5.1 years for IAD compared to 5.8 years for the continuous treatment arm).
- Published results of this and other ongoing studies are awaited to determine the further benefits and safety of IAD in men with advanced disease.

Second line hormone therapy

- Some patients will respond to second-line hormone therapy with the addition of an anti-androgen, to achieve combined androgen blockade (CAB) With further progression anti-androgen withdrawal responses are seen in approximately 25% of cases who have been treated with first-line CAB or have had substantial (>1 year response) to second-line CAB.
- A common second-line treatment is the addition of an anti-androgen. A retrospective analysis of 122 patients who received the addition of bicalutamide 50 mg to goserelin for PSA and clinical progression showed a >50% decrease in PSA concentration in 30% of patients (responders) and a reduction in PSA concentration in 75% of all patients. The median duration of response from start of bicalutamide 50 mg was 291 days for responders and 193 days for the population as a whole. Those patients with a short duration of response to goserelin monotherapy (<1 year) appeared less likely to respond to CAB with the addition of bicalutamide 50 mg than those who had a longer response (1–2 years).
    - There are reports of PSA responses as a result of anti-androgen withdrawal in men whose disease is progressing on CAB. A recently reported multi-institutional, prospective study demonstrated PSA decreases of ≥50% in 21% (16% to 27%) of 210 men with progressive prostate cancer who discontinued the anti-androgen component of their CAB therapy [Sartor AO, *et al* 2008].
    - Median PFS was 3 months; however, 19% of responders had 12-month or greater progression-free intervals. Longer duration of initial anti-androgen use was shown to be a significant predictor of PSA response.

Side-effects of hormone therapy

- LHRH agonists and GnRH antagonists have a similar tolerability profile: side-effects include erectile dysfunction and loss of libido, reduction in bone mineral density, hot flushes and sweating, and weight gain and injection-site reactions (GnRH antagonists) and metabolic syndrome.
- Anti-androgen side-effects include gynaecomastia and breast tenderness. Mild to moderate gynaecomastia (68.8%) and breast pain (73.6%) are the most common adverse events described.

Castration Resistant Prostate Cancer: Management Options

Prostate cancers that progress despite castrate levels of testosterone are considered castration resistant and not hormone refractory. This is based on findings that the cancer is not uniformly refractory to further hormonal manipulation. Castration-resistant prostate cancer (CRPC), which is still hormone sensitive, has been clearly characterized, with new drugs targeting the androgen receptor, such as enzalutamide, or androgen biosynthesis, via CYP 17 inhibition, such as abiraterone acetate

There are a number of options for therapy for CRPC but the exact sequencing remains undetermined and will depend on both tumour characteristics (e.g. Gleason Score, PSA velocity) patient comorbidities and fitness for therapy and patient choice. The results of sequencing studies are awaited.

Further hormone therapies for CRPC

- Corticosteroids alone have definite activity against prostate cancer (approximately 20% response rate) and provide significant palliation in terms of anorexia, pain and depression. The optimal drug and dose have not been determined, but even prednisone at a dose of 5 mg bid resulted in subjective and PSA responses in one randomised trial [Tannock IF, *et al* 1996].
- Dexamethasone has been shown to be effective for men with progressive metastatic CRPC [Venkitaraman R, *et al* 2008]. In a study of 102 patients treated with oral dexamethasone (0.5 mg daily), 49% had a confirmed PSA response. The median time to PSA progression for the entire cohort was 7.4 (1-28) months and in responders, the median duration of the PSA response was 11.6 (1-24) months.
- Abiraterone acetate is a non-steroidal ester that selectively and irreversibly inhibits both 17α-hydroxylase and the C17, 20-lyase function of CYP17A1, a cytochrome involved in the production of dehydroepiandrosterone (DHEA) and androstenedione (precursors of testosterone). Abiraterone inhibits androgen biosynthesis at all three key sources in prostate cancer: the testes, adrenal glands and prostate tumour cells. It is administered in combination with glucocorticoids to prevent elevated levels of other steroid hormones and associated fluid balance abnormalities.
- Abiraterone in combination with prednisolone (5 mg twice daily) has been investigated in the pre-docetaxel setting in the COU 302 study in asymptomatic or minimally symptomatic men with a performance status of 0 to 1 and progressive castration resistant prostate cancer [Ryan CJ, *et al* 2013]. This multi-centre, double blind study randomised 1088 patients to abiraterone acetate 1000 mg daily and prednisolone versus placebo plus prednisolone. The study was unblinded after a planned interim analysis that was performed after 43% of the expected deaths had occurred. Results showed a significant improvement in radiographic progression-free survival with a median of 16.5 months with abiraterone-prednisone and 8.3 months with prednisone alone, HR 0.53; 95% CI 0.45 to 0.62; P<0.001). Over a median follow-up period of 22.2 months, overall survival was improved with abiraterone-prednisone (median not reached, vs. 27.2 months for prednisone alone; HR, 0.75; 95% CI, 0.61 to 0.93; P=0.01) but did not cross the efficacy boundary. Abiraterone-prednisone showed superiority over prednisone alone with respect to time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, prostate-specific antigen progression, and decline in performance status. Toxicity included mineralocorticoid-related adverse events and abnormalities on liver-function testing were more common with abiraterone-prednisone, but mainly grade 1 or 2.
- Oestrogen therapy with DES demonstrated a comparable efficacy to castration in 1977 and was one of the first initial promising hormone manipulations. However the first Veterans studies showed that early treatment of advanced prostate cancer with DES 5 mg did not increase OS when compared to placebo, as the drug was associated with an increased incidence of cardiovascular deaths [Byar DP 1972].
- A second study compared the DES 5 mg dose to 1 mg and the results showed that this lower dose was equally effective but was associated with a much lower incidence of cardiovascular deaths. The risk of cardiovascular events may require the concomitant use of aspirin/anticoagulants [Robinson MR (a), *et al* 1995].
- Other new agents such as enzalutamide and orteronel are currently under evaluation in the prechemotherapy setting.
- There is now evidence for further use of hormone therapies after docetaxel (see below) The choice between these drugs or the use of second line chemotherapy remains unclear and sequencing studies are urgently awaited.

- Abiraterone has also been investigated in the COU 301 study [Fizazi K, *et al* 2012]. This was multicentre, prospective double blind randomised trial of 1195 patients with metastatic CRPC who were randomly assigned (ratio2:1) abiraterone acetate 1000 mg daily plus prednisolone (5 mg twice daily) or placebo and prednisolone (5 mg twice daily). All patients had progressive disease after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). After a median follow-up of 20.2 months, the median survival in the abiraterone group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, P < 0.001). The median time to PSA progression was 8·5 months, CI 8·3-11·1, in the abiraterone group vs. 6·6 months, 5·6-8·3, in the placebo group; HR 0·63, 0·52-0·78; p<0·0001), median radiologic progression-free survival (5·6 months, 5·6-6·5, vs. 3·6 months, 2·9-5·5; HR 0·66, 0·58-0·76; p<0·0001), and proportion of patients who had a PSA response (235 [29·5%] of 797 patients vs. 22 [5·5%] of 398; p<0·0001) were all improved in the abiraterone group compared with the placebo group. The most common grade 3-4 adverse events were fatigue (72 [9%] of 791 patients in the abiraterone group vs. 41 [10%] of 394 in the placebo group), anaemia (62 [8%] vs. 32 [8%]), back pain (56 [7%] vs. 40 [10%]), and bone pain (51 [6%] vs. 31 [8%]).The benefit was observed irrespective of age, baseline pain intensity, and type of progression.
- Enzalutamide is a novel oral antiandrogen that targets multiple steps in the androgen-receptor-signalling pathway and has shown a significant survival benefit for men with CRPC following docetaxel chemotherapy
- In the AFFFIRM study 1199 men with castration resistant prostate cancer after docetaxel chemotherapy were randomly assigned them, in a 2:1 ratio, to receive oral enzalutamide at a dose of 160 mg per day or placebo (399 patients) [Scher HI, *et al* 2012]. The study was stopped after a planned interim analysis at the time of 520 deaths. The median overall survival was 18.4 months (95% 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). All the secondary objectives were in favour of enzalutamide. the proportion of patients with a reduction in the PSA level by 50% or more (54% vs. 2%, P<0.001), the soft-tissue response rate (29% vs. 4%, P<0.001), the quality-of-life response rate (43% vs. 18%, P<0.001), the time to PSA progression (8.3 vs. 3.0 months; hazard ratio, 0.25; P<0.001), radiographic progression-free survival (8.3 vs. 2.9 months; hazard ratio, 0.40; P<0.001), and the time to the first skeletal-related event (16.7 vs. 13.3 months; hazard ratio, 0.69; P<0.001). Rates of fatigue, diarrhoea, and hot flashes were higher in the enzalutamide group with a lower incidence of grade 3-4 side effects in the enzalutamide arm. Seizures were reported in five patients (0.6%) receiving enzalutamide.

Chemotherapy

An alternative treatment for advanced CRPC is chemotherapy. Docetaxel is now recommended as first line chemotherapy.

Side-effects of chemotherapy depend on the exact treatment regime, but usually include fatigue, nausea and vomiting, diarrhoea, hair loss and bone marrow suppression with increased susceptibility to infection. Specific therapies to handle these side-effects may be necessary to improve the patient's quality of life.

- A prospective study by Tannock in 1996 compared the benefits of mitoxantrone 12 mg/m² every 3 weeks plus prednisone 5 mg twice-daily with prednisone alone in 161 men with symptomatic HRPC [Tannock IF, *et al* 1996].
    - The primary endpoint was palliative response defined as a 2-point decrease in pain as assessed by a 6-point pain scale.
    - There was a significant advantage to the chemotherapy combination with a 29% pain response compared to 12% with steroids alone.
    - The duration of palliation was 43 weeks versus 18 weeks ($p<0.0001$) in favour of mitoxantrone and prednisone.
    - There was no difference in PSA or survival. It was therefore concluded that chemotherapy with mitoxantrone and prednisone provides palliation for some patients with symptomatic HRPC.
- The TAX 327 study randomised 1006 men with advanced prostate cancer to three treatment regimens [Tannock IF, *et al* 2004].
    - These were docetaxel 75 mg/m² administered every 3 weeks, docetaxel 30 mg/m² every week and mitoxantrone 12 mg/m² every 3 weeks, each with prednisone 5 mg twice-daily.
    - Initial results were published in 2004 and showed a significant improvement in median survival with 3-weekly docetaxel plus prednisolone (18.9 months), compared with the comparator arm of mitoxantrone plus prednisolone (16.5 months) ($p<0.001$).
    - A total of 45% of those in the docetaxel arm had a PSA reduction ≥50% compared to 32% of those having mitoxantrone ($p=0.0005$).
    - Increased benefits in pain response (35% versus 22%, $p=0.01$) were demonstrated in favour of docetaxel.
    - Quality of life was improved in 13% of patients receiving mitoxantrone, 22% of patients receiving 3-weekly docetaxel ($p=0.009$) and 23% of patients receiving weekly docetaxel ($p=0.005$).
- Further results have recently been reported and the survival benefit with 3-weekly docetaxel has persisted with extended follow-up [Berthold DR, *et al* 2008].
    - Median survival was 19.3 months for 3-weekly docetaxel versus 16.3 months in the mitoxantrone arm ($p=0.006$) with respective 3-year survival figures of 17.9% versus 13.7% in favour of docetaxel.
    - This study has confirmed the benefits of docetaxel chemotherapy.
    - The extended analysis of the TAX 327 study included subgroup analyses and demonstrated survival benefits for men both <65 years and >75 years of age.

- Cabazitaxel is a novel tubulin-binding taxane drug with antitumour activity in docetaxel-resistant prostate cancers. Positive results were seen for cabazitaxel from a large prospective randomised, phase III trial (TROPIC study) [de Bono JS, *et al* 2010]. In this study, 755 men with metastatic castration-resistant prostate cancer whose disease had progressed during or after treatment with a docetaxel-containing regimen were treated with 10 mg oral prednisone daily, and were randomly assigned to receive either 12 mg/m2 mitoxantrone intravenously or 25 mg/m2 cabazitaxel intravenously every 3 weeks. An overall survival benefit (15.1 vs. 12.7 months, P < 0.0001) was observed in the cabazitaxel arm. There was also a significant improvement in PFS (2.8 vs. 1.4 months, P < 0.0001), objective response rate according to RECIST criteria (14.4% vs. 4.4%, P <0.005), and PSA response rate (39.2% vs. 17.8%, P < 0.0002). The most common clinically significant grade 3 or higher adverse events were neutropenia (cabazitaxel, 303 [82%] patients vs mitoxantrone, 215 [58%]) and diarrhoea (23 [6%] vs. one [<1%]). 28 (8%) patients in the cabazitaxel group and five (1%) in the mitoxantrone group had febrile neutropenia.

Bone targeted agents

Bisphosphonates

- The benefits of zoledronic acid, in combination with hormone therapy have been investigated in a study by Saad in men with HRPC and bone metastases [Saad F, *et al* 2002]. This was a multicentre, randomised, placebo-controlled trial evaluating the efficacy of zoledronic acid 4 mg administered every 3 weeks in 422 patients with HRPC for 15 months, with an option to continue for an additional 9 months.
    - At the 2-year analysis, treatment with zoledronic acid was found to significantly reduce the percentage of patients with at least one skeletal-related event (SRE; defined as radiation for bone pain or to prevent pathological fracture/spinal cord compression; pathological fracture; spinal cord compression; surgery to bone; change in antineoplastic therapy) compared with placebo (38% versus 49%; p=0.028). All SREs were delayed.
    - Zoledronic acid also significantly delayed the time to first SRE by around 6 months (median 488 versus 321 days; p=0.009). Furthermore, patients in the zoledronic acid group had consistently lower incidences of all types of SRE than the placebo group. Pain scores were consistently lower in patients taking zoledronic acid 4 mg than placebo, and significantly at 3, 9, 18, 21 and 24 months (p<0.05).
- In the MRC PR05 and PR04 trials, men with advanced prostate cancer were randomised to sodium clodronate 2080 mg/day or placebo for up to 3 years (metastatic disease) or up to 5 years (non-metastatic disease) [Dearnaley DP, *et al* 2009].
    - A benefit of sodium clodronate versus placebo in men with metastatic disease was demonstrated for OS (HR: 0.77; 95%CI: 0.60–0.98; p=0.032).
    - However, no benefit of sodium clodronate versus placebo for OS in men with non-metastatic disease was demonstrated (HR: 1.12; 95%CI: 0.89–1.42; p=0.94).

Side-effects

- Bisphosphonates are generally well tolerated.
- Side-effects include: hypophosphataemia, anaemia, influenza-like symptoms, gastrointestinal effects, headache, conjunctivitis, very rarely osteonecrosis of jaw and renal impairment.
- To avoid this, patients on bisphosphonates should avoid dental surgery and extractions. If required this should be performed before starting treatment.
- In the study by Saad *et al*., zoledronic acid was generally well-tolerated [Saad F, *et al* 2002]:
    - Bone pain, nausea and constipation were reported most frequently both by patients receiving zoledronic acid and by those in the placebo group
    - In the zoledronic acid group, fatigue, anaemia, myalgia, fever and lower limb oedema occurred in at least 5% more patients than that observed in the placebo group
- In uncommon cases, patients treated with intravenous zoledronic acid have reported osteonecrosis of the jaw (ONJ) [Marx RE, *et al* 2005].
    - Risk factors associated with the development of ONJ include concomitant chemotherapy and corticosteroids, the patient's underlying disease, and other co-morbid risk factors (e.g. anaemia, local infection, pre-existing oral disease) [Zometa SPC].

RANK ligand inhibitors

- Denosumab is a fully human monoclonal antibody directed against RANKL and a key mediator of osteoclast formation, function, and survival.
- The efficacy and safety of denosumab (n = 950) compared with zoledronic acid (n=951) in patients with metastatic CRPC was assessed in a large randomised phase III trial [Fizazi K, *et al* 2011]. In this multicentre phase 3 study, 1904 men with CRPC and no previous exposure to intravenous bisphosphonate were randomised to receive 120 mg subcutaneous denosumab plus intravenous placebo, or 4 mg intravenous zoledronic acid plus subcutaneous placebo, every 4 weeks until the primary analysis cutoff date. Supplemental calcium and vitamin D were strongly recommended. Median duration on study at primary analysis cutoff date was 12·2 months (IQR 5·9-18·5) for patients on denosumab and 11·2 months (IQR 5·6-17·4) for those on zoledronic acid.
- Results showed that denosumab was superior to zoledronic acid in delaying or preventing SREs, as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 vs. 17.1 months, respectively (HR 0.82; P = 0.008). Denosumab also extended time to first and subsequent on-study SRE (HR 0.82; P = 0.008). Both urinary NTX and BAP were significantly suppressed in the denosumab arm compared with the zoledronic acid arm (P < 0.0001 for both). There was no overall survival benefit seen. Adverse events were recorded in 916 patients (97%) on denosumab and 918 patients (97%) on zoledronic acid, and serious adverse events were recorded in 594 patients (63%) on denosumab and 568 patients (60%) on zoledronic acid. More events of hypocalcaemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 [6%]; p<0·0001). Osteonecrosis of the jaw occurred infrequently (22 [2%] vs. 12 [1%]; p = 0·09).

Systemic radionuclide therapy

Strontium

- Metastatic pain can be palliated effectively with systemic radionuclide therapy with strontium chloride.
- Relief of bone pain starts within 2 weeks. Possible initial bone pain flare may occur within 2 days, lasting 2–4 days.
    - Pain relief lasts 4–15 months.
    - 75–80% of patients experience significant palliation of pain.
- A Canadian collaborative study showed significant improvement in quality of life, increased time to further metastases, significant reduction in the amount of additional radiotherapy needed, and significant falls in PSA and alkaline phosphatise [Porter AT, *et al* 1993].
- Strontium is not associated with improvements in OS [Brundage MD, *et al* 1998].
- Four randomised clinical trials have reviewed the use of strontium [Robinson RG (b), *et al* 1995].
    - One trial reported significant improvement in pain control, two trials reported fewer new sites of pain.
    - One trial showed no significant difference in pain control compared to a placebo but an improved 2-year survival rate.
- A randomised clinical trial examining strontium versus placebo found a significant increase in median time to progression, but no significant effects on median OS or clinical response [Tu SM, *et al* 2001].

Side-effects

- The most notable side-effect of strontium is mild haematological suppression with a fall in circulating platelet and leukocyte counts recognised in most patients.
    - With usual therapeutic doses, platelets typically fall by 30% and leucocytes by 20%.
    - Clinically significant toxicity is rare, but its use is not recommended in patients with severely compromised bone marrow, platelet count <100, superscan prior to therapy, or impending spinal cord progression.

Radium 223

- Radium-223 dichloride (radium-223) is an alpha emitter which selectively targets bone metastases with alpha particles.
- The efficacy and safety of radium-223 was assessed in the ALSYMPCA study [Parker C, *et al* 2013]. In this multicentre, phase 3, randomized, double-blind, placebo-controlled study, 902 men , who had received, were not eligible to receive, or declined docetaxel, were randomly assigned in a 2:1 ratio, to receive six injections of radium-223 (at a dose of 50 kBq per kilogram of body weight intravenously) or matching placebo; one injection was administered every 4 weeks. In addition, all patients received the best standard of care. At the interim analysis, which involved 809 patients, radium-223, as compared with placebo, significantly improved overall survival (median, 14.0 months vs. 11.2 months; hazard ratio, 0.70; 95%CI, 0.55 to 0.88; two-sided P=0.002). The updated analysis involving 921 patients confirmed the radium-223 survival benefit (median, 14.9 months vs. 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83; P<0.001). Assessments of all main secondary efficacy end points also showed a benefit of radium-233 as compared with placebo. Radium-223 was associated with low myelosuppression rates and fewer adverse events.

Palliative Care

Overview

- Radiotherapy has been a mainstay in the palliation of painful metastatic bone lesions. Palliative radiotherapy can also aid other complications of metastatic disease, such as compression of the spinal cord or a nerve root, haematuria, ureteric obstruction, perineal discomfort caused by the local progression of prostate cancer, and symptomatic metastatic lymphadenopathy.

Clinical evidence

- Good evidence for the role of radiotherapy in palliation comes from McQuay *et al*. This systematic review covered 20 trials, which reported on 43 different radiotherapy fractionation schedules, and eight studies of radioisotopes [McQuay HJ, *et al* 1997].
    - Radiotherapy produced complete pain relief at 1 month in 395 out of 1580 (25%) patients, and at least 50% relief in 788 out of 1933 (41%) patients at some time during the trials.
    - In the largest trial, which included 759 patients, 52% achieved complete pain relief within 4 weeks and the median duration of complete relief was 12 weeks.
    - The study found no difference between the use of radioisotopes (such as strontium) and EBRT for generalised disease, a finding supported by the work of Quilty *et al* [Quilty PM, *et al* 1994].
    - In this latter study, 284 patients with prostate cancer and painful bone metastases were treated with local or hemi-body radiotherapy or strontium. Median survival was non-significantly different between groups (33 weeks with strontium versus 28 weeks with radiotherapy; p=0.1) [Quilty PM, *et al* 1994].
    - Both radiotherapy and strontium provided effective pain relief that was sustained for 3 months in 63.6% of patients after hemi-body radiotherapy compared with 66.1% of patients after strontium, and in 61% of patients after local radiotherapy compared with 65.9% of patients in the comparable strontium group.
    - Fewer patients reported new pain sites after strontium than after local or hemi-body radiotherapy ($p<0.05$) and radiotherapy to a new site was required by 12 patients in the local radiotherapy group compared with two receiving strontium ($p<0.01$).

Ongoing Support

The MDT team should ensure regular communication with the primary care team.

This may mean:

- Timely provision of detailed discharge or outpatient summaries
- Explanation of why a treatment route has been decided upon
- The patient's response to the chosen treatment
- Sharing of protocols
- Online educational resources
- Agreement on prescribing policies
- Provision of contact numbers for requests for information

The local patient support network, e.g. partner/family, must be included in the information/education process through the use of:

- Patient information materials
- Audio visual materials such as videos, DVDs and Web-based information

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