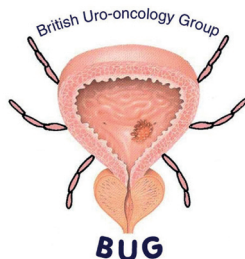


MDT (Multi-disciplinary Team) Guidance for Managing Prostate Cancer

2nd Edition (November 2009)

Produced by:

- British Uro-oncology Group (BUG)
- British Association of Urological Surgeons (BAUS): Section of Oncology
- British Prostate Group (BPG)



This guidance has been supported by educational grants from Ferring Pharmaceuticals, Novartis and sanofi-aventis. The development and content of this guidance has not been influenced in any way by the supporting companies.

Abbreviations

3D-CRT: three-dimensional conformal radiotherapy
ADT: androgen deprivation therapy
BPH: benign prostatic hyperplasia
CAB: combined androgen blockade
CHHiP: Conventional or Hypofractionated High Dose IMRT for Prostate Cancer
CI: confidence interval
CPA: cyproterone acetate
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
GnRH: gonadotrophin-releasing hormone
HDR: high dose rate
HIFU: high-intensity focused ultrasound
HR: hazard ratio
HRPC: hormone-refractory prostate cancer
IMRT: intensity modulated radiotherapy
IPSS: International Prostate Symptom Score
LDR: low dose rate
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
PFS: progression-free survival
PLCO: Prostate, Lung, Colorectal and Ovarian
Protect: Prostate Testing for Cancer and Treatment
PSA: prostate-specific antigen
RCT: randomised controlled trial
SRE: skeletal-related events
STAD: short-term androgen deprivation
TRUS: transrectal ultrasound
TURP: transurethral resection of the prostate

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	(Oncology pharmacists)
Radiologists	(Social workers)
Histopathologists	(Dieticians)

- According to the UK-based Integrated Care Network, the move to true integrated practice can add value in the following ways:¹
 - 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.

Figure 1: Summary of the definition of prostate cancer stages

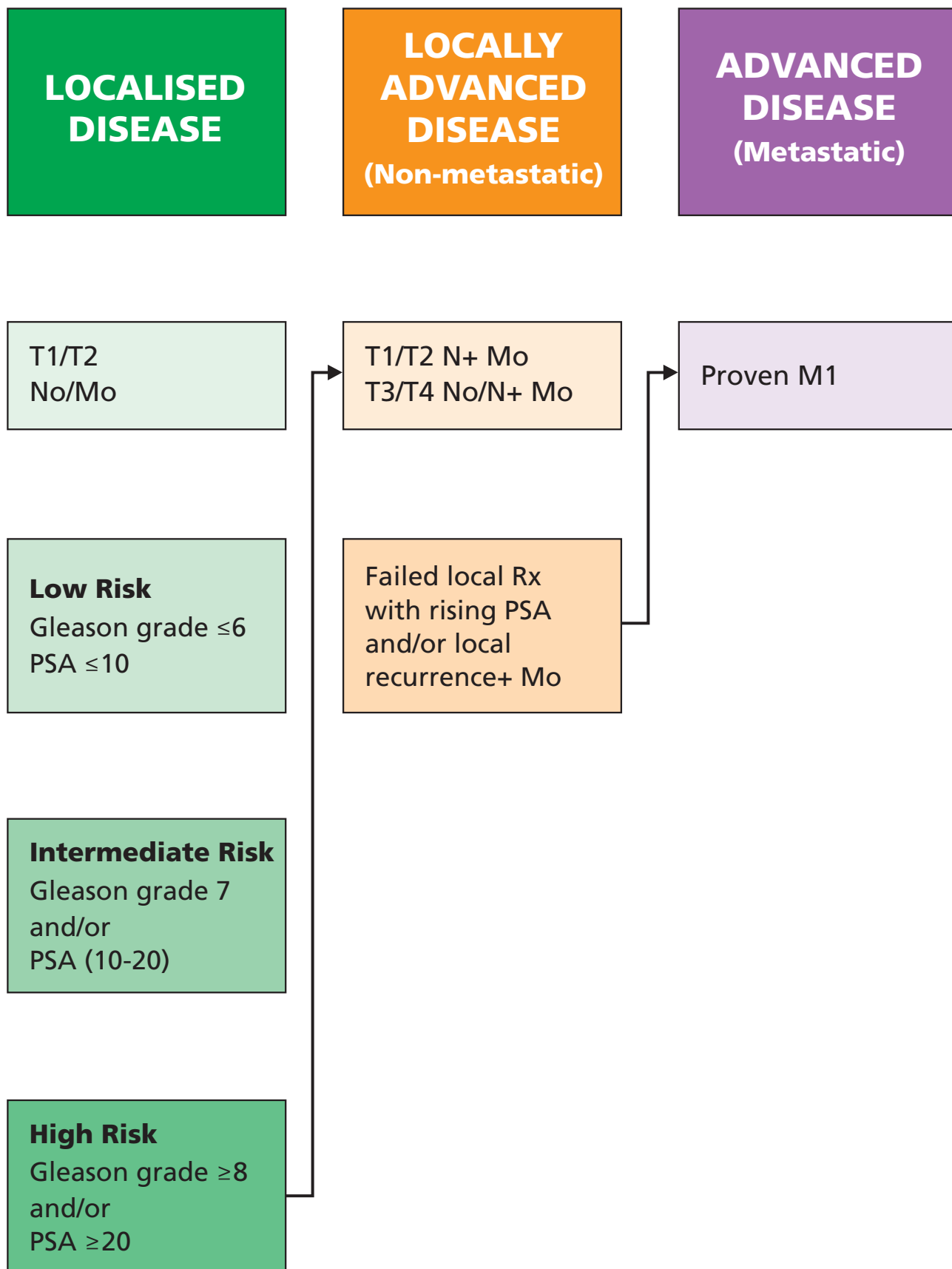


Figure 2: Treatment algorithm for localised disease

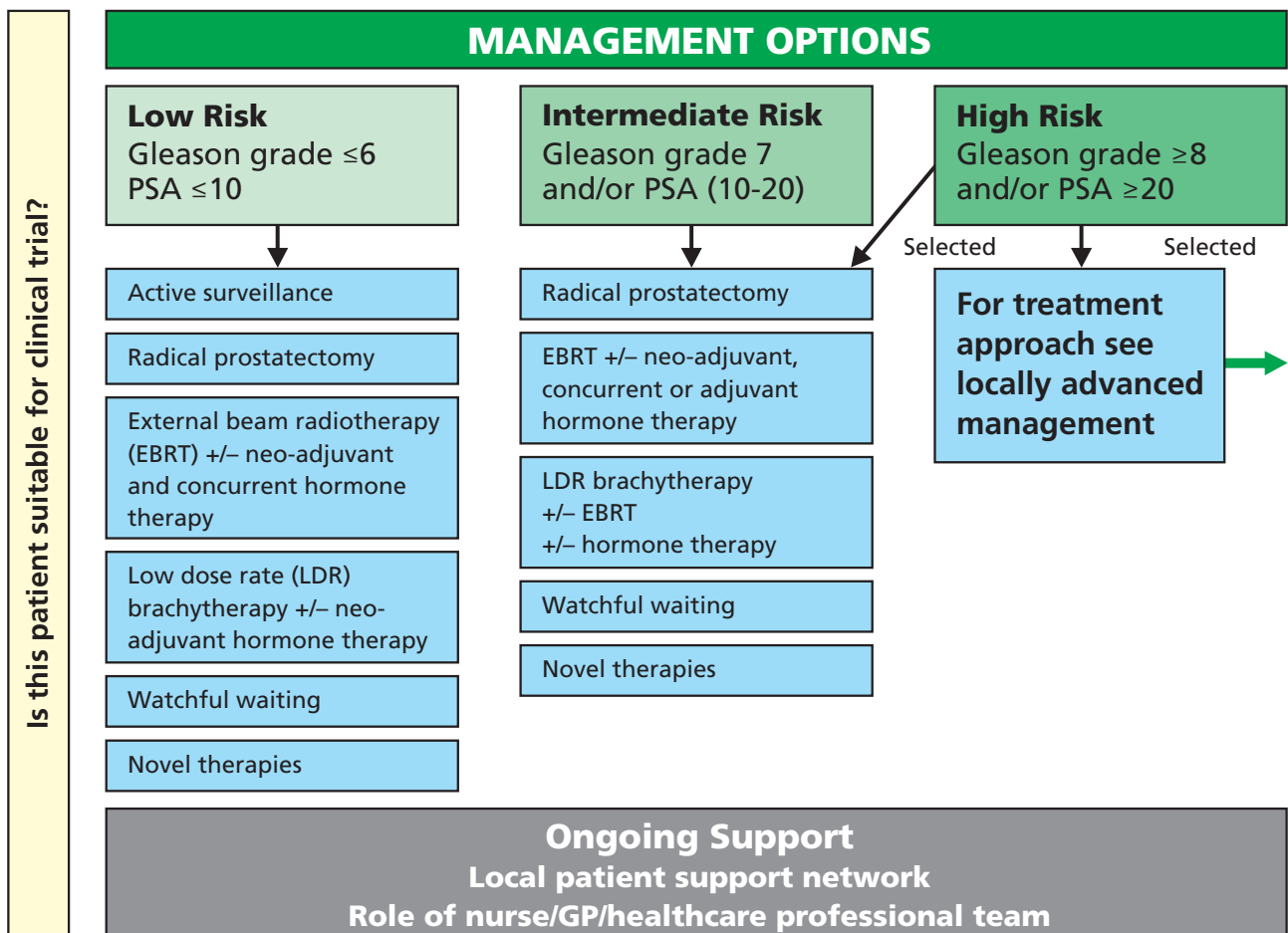
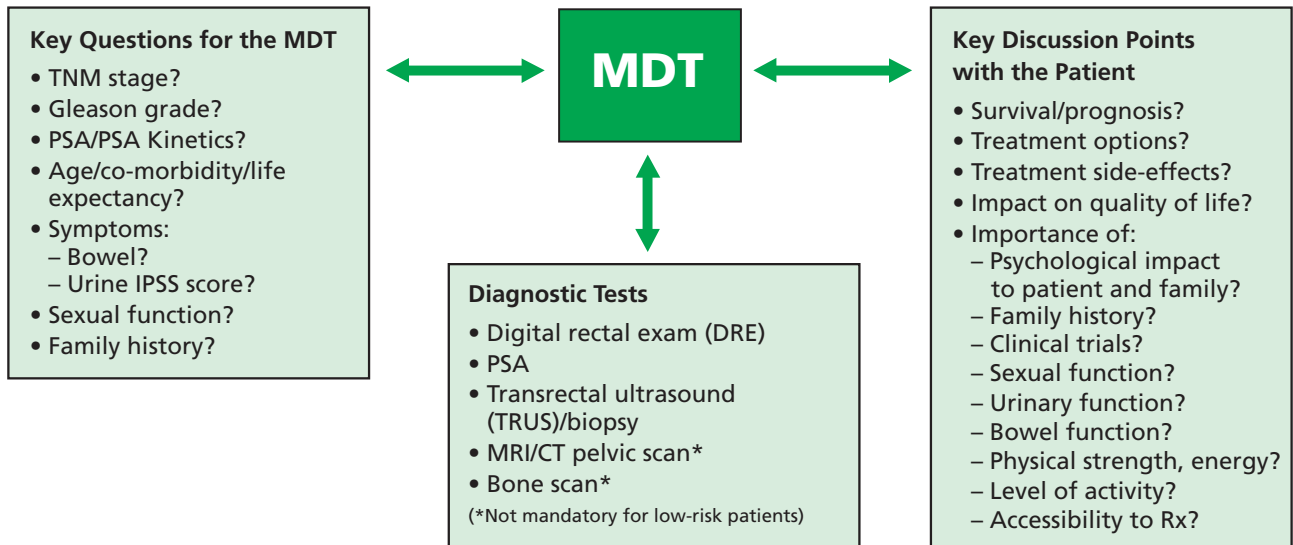


Figure 3: Treatment algorithm for locally advanced (non-metastatic) disease

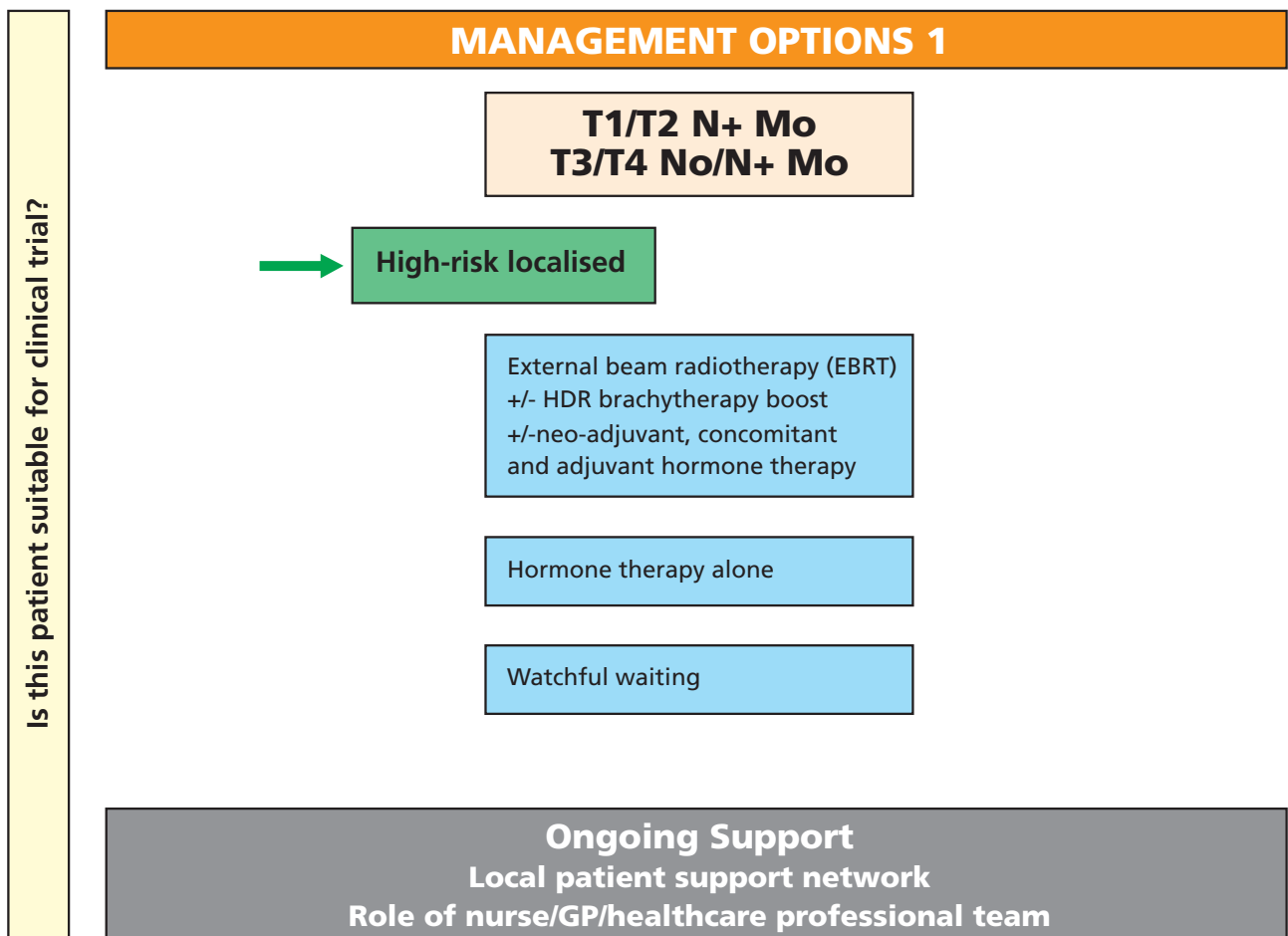
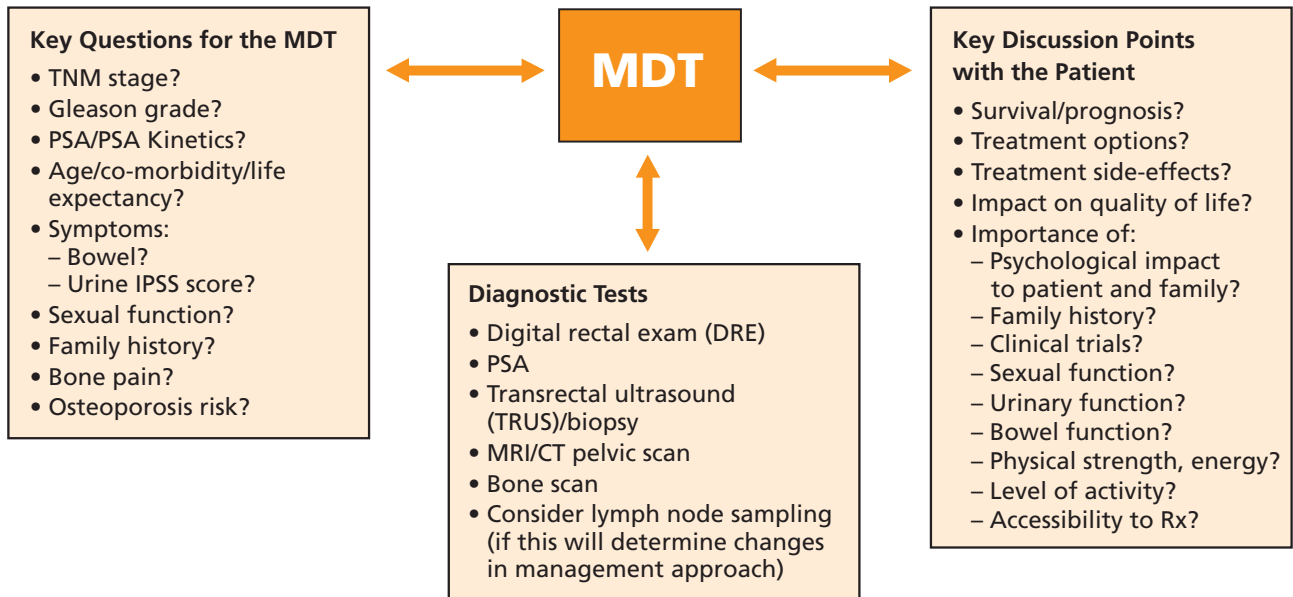


Figure 3: Treatment algorithm for locally advanced (non-metastatic) disease (cont.)

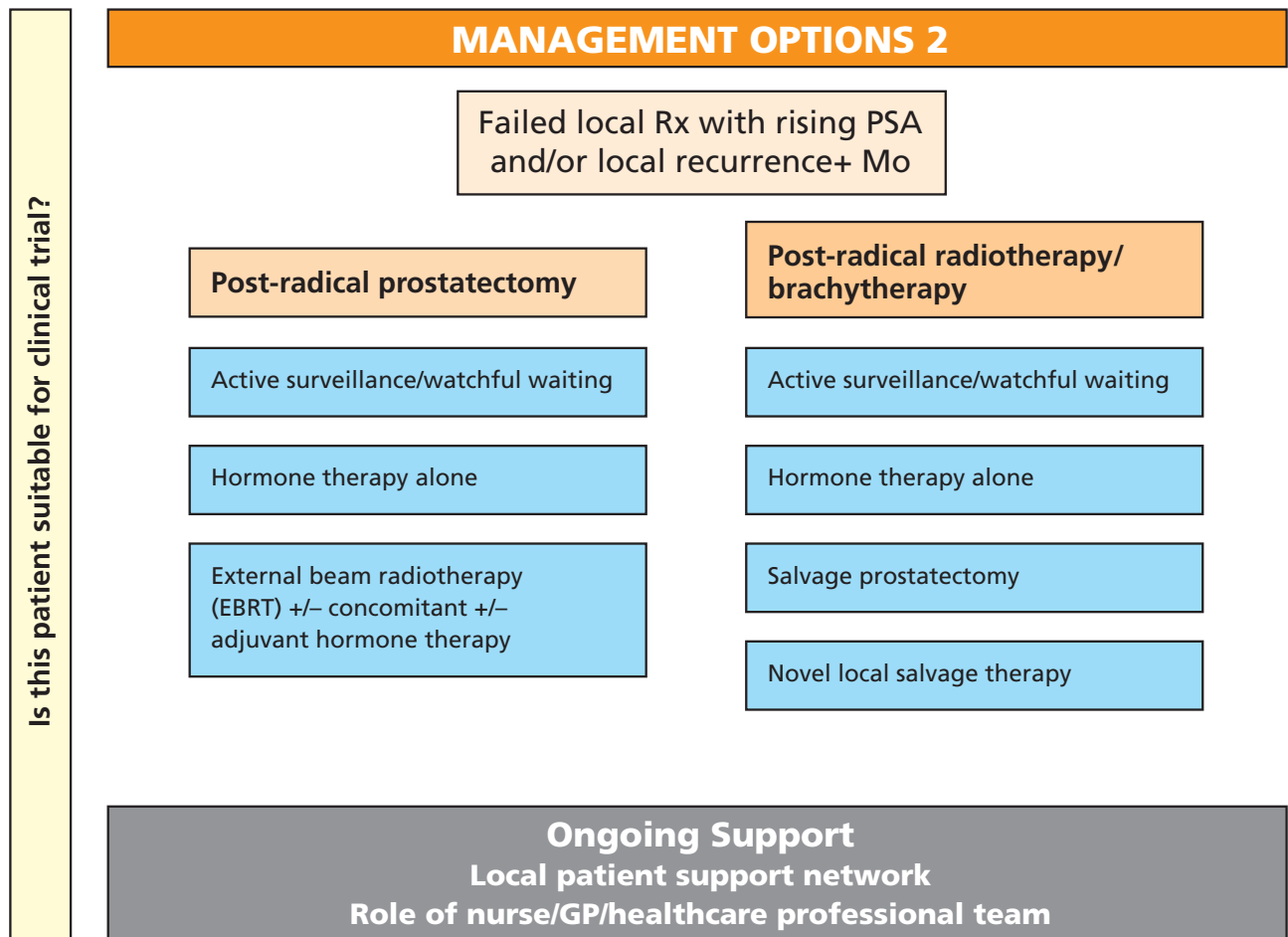
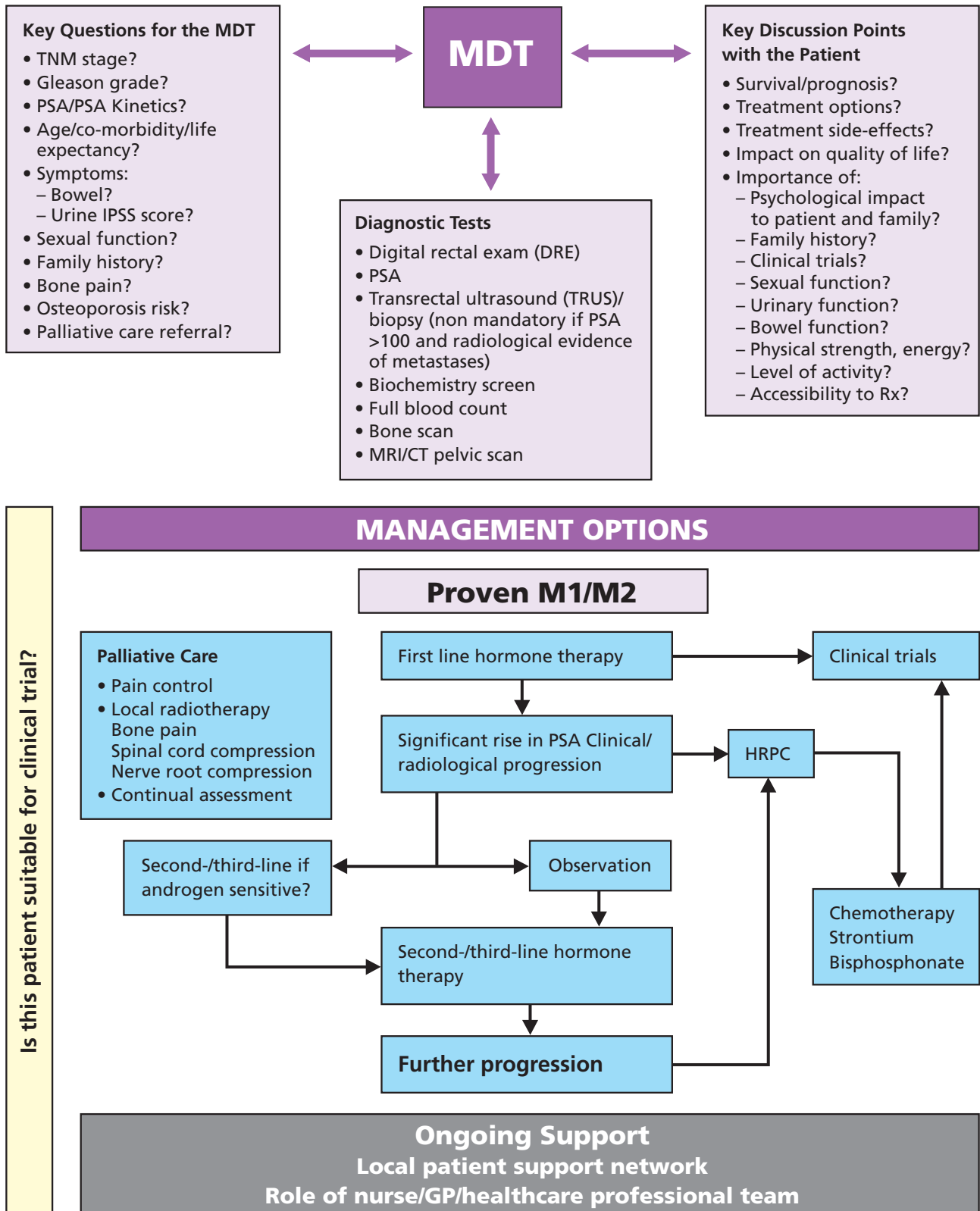


Figure 4: Treatment algorithm for advanced (metastatic) disease



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 (allowing for individual clinical discretion and patient involvement in decision-making) ensures that the patient's journey is monitored and assessed as a single entity.

Approach within the MDT

Key questions for the MDT

- TNM stage?
- Gleason grade?
- Prostate-specific antigen (PSA) concentration?
- Risk group (according to National Comprehensive Cancer Network [NCCN] guidelines)?
- Age/co-morbidity/life expectancy?
- Symptoms:
 - International Prostate Symptom Score (IPSS), bowel, urinary?
- Sexual function?
- Bone pain?
- Osteoporosis risk?
- Family history?
- Clinical trials?

- The MDT is an essential part of cancer management. However, there are often difficulties in knowing which patients to discuss, 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.²
- 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.³
- The possibility of including a patient in a relevant clinical trial should not be forgotten.

Approach to the Patient

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 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:⁴
 - 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. It is felt that robust evidence is lacking concerning whether screening results in a reduction in mortality from the disease.
- 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),⁵ the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial in the US⁶ and the UK-based Prostate Testing for Cancer and Treatment (ProtecT) study.⁷ 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 7 years.⁶
 - In contrast, the ERSPC trial found that PSA screening was associated with a 20% relative reduction in prostate cancer mortality at a median follow-up of 9 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 a false positive result.⁵
 - 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.⁷
- 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 is compiling equivalent UK data.⁸
 - Men of Chinese and Japanese origin have a low incidence of disease.
- 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.⁹
 - 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.

- 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.¹⁰
- 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

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

- As an independent variable, PSA concentrations are a better predictor of cancer than suspicious findings on DRE or transrectal ultrasound (TRUS).^{11, 12}
- 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.^{13, 14}
- 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.^{15–17}
- Asymptomatic patients who request a PSA test should be counselled before the procedure for the following reasons:¹⁸
 - 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 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 race¹⁹

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).²⁰

Prostatitis can cause an increase in PSA concentration, which can be reduced to within a normal range with antibiotic treatment.^{21, 22}

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

Infection – elevated PSA levels can be seen beyond 6 months in up to 50% of patients when associated 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.²³

Table 3: Probability of prostate cancer based on total and percentage free PSA²³

	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.²⁴

TRUS

- TRUS detects 50% more patients with prostate cancer than physical examination alone,^{25, 26} 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.^{26–28} Therefore, TRUS is mainly used to aid biopsy.

Biopsy and tumour grading

- 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.²⁹ 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.²⁹ 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 biopsy is indicated, a minimum of 10 biopsies should be obtained, according to the volume of the prostate. Biopsies should be performed under local anaesthetic and antibiotic cover.³⁰
- 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%.³¹

Magnetic Resonance Imaging (MRI)

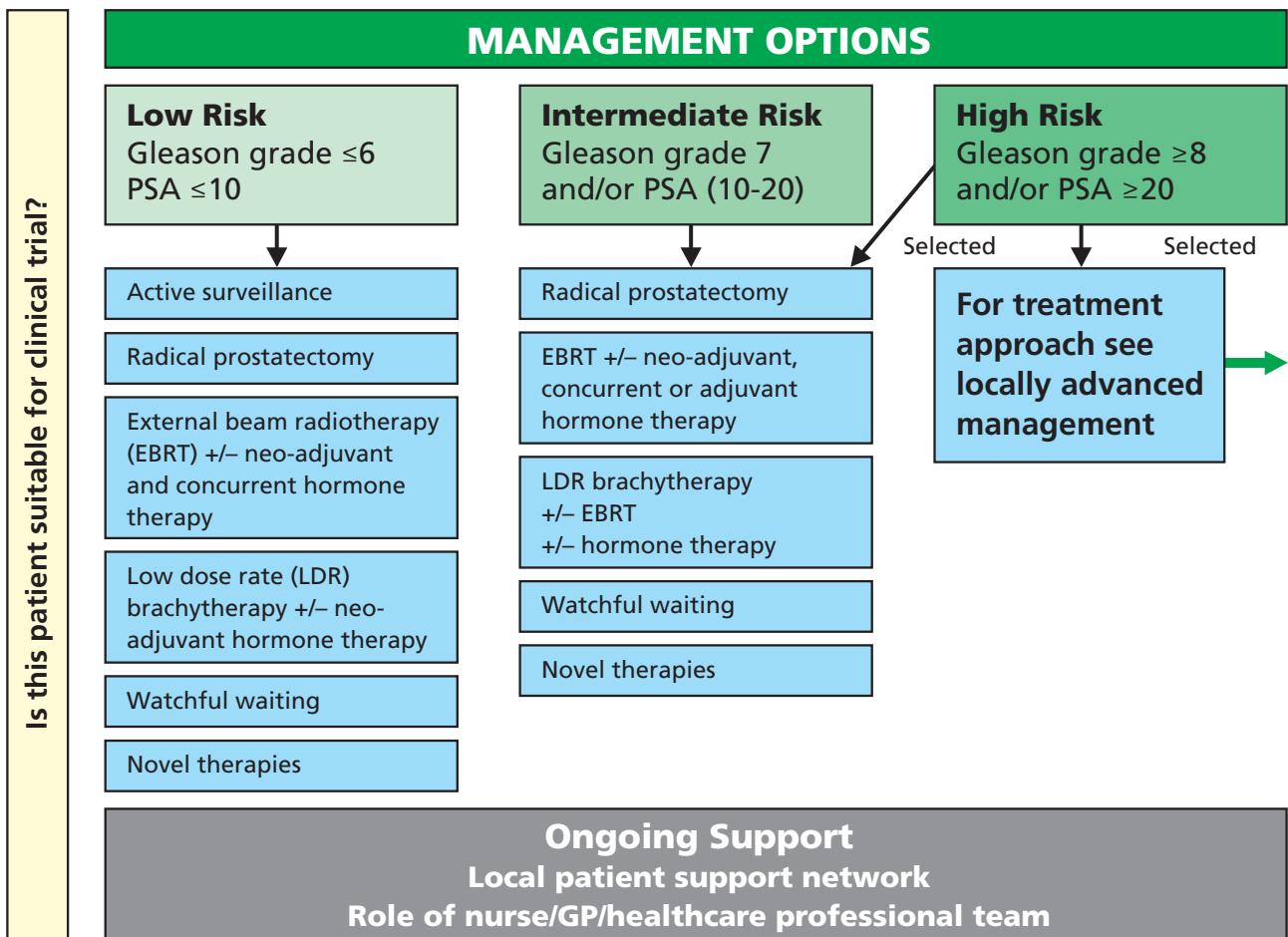
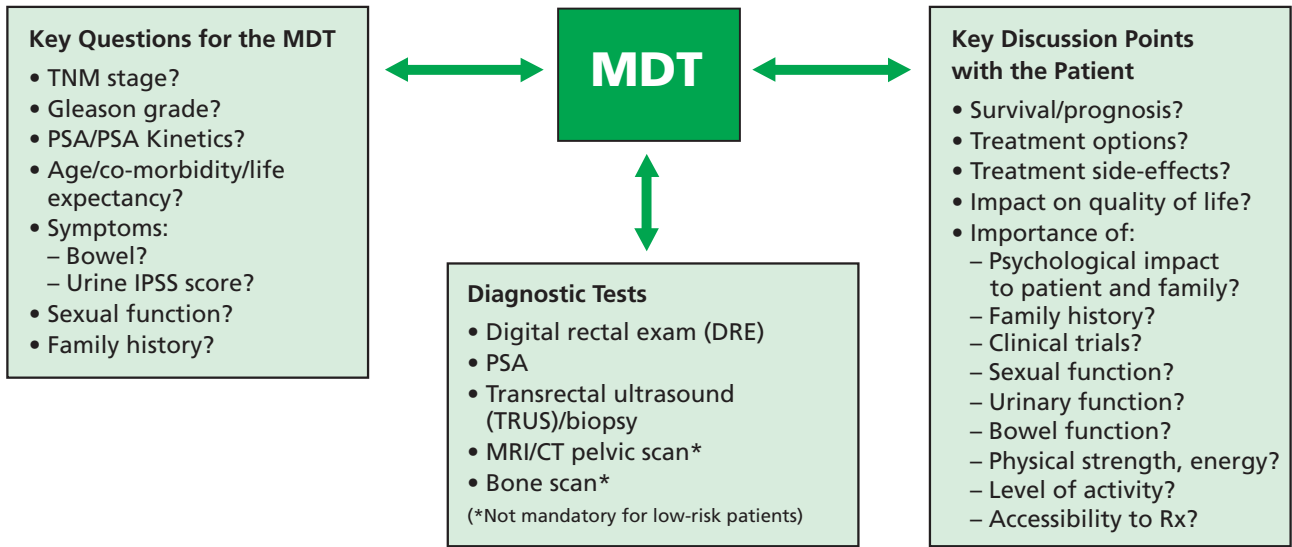
- The classification used for staging prostate cancer is the internationally approved system recommended by the Union International Contra Cancer (available at: www.uicc.org).
- TNM staging, Gleason score, and PSA concentration facilitate estimation of the risk of extracapsular disease and lymph node 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.²⁹
- Body coil MRI is sensitive and specific in identifying extracapsular extension of prostate cancer in patients with high- or intermediate-risk disease.³²
- NICE concludes:²⁹
 - MRI is now the most accurate and commonly-used imaging technique for tumour-staging men with prostate cancer. Many of the original publications used now outdated MRI technology, and the accuracy reported for MRI is improving, typically with endorectal coil imaging at 1.5 Tesla.
 - After transrectal prostate biopsy, intra-prostatic haematoma can affect image interpretation for at least 4 weeks.
 - Magnetic resonance spectroscopy (MRS) is an experimental technique based on the concentration of metabolites such as choline and citrate in the prostate gland. Prostate cancer alters the concentrations of these metabolites and this may be used to find areas of tumour activity. MRS is not recommended for men with prostate cancer except in the context of a clinical trial.

Bone scans and lymph node sampling

- Bone scans (particularly in patients with PSA concentration >20 ng/ml) and lymph node biopsies 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%.³³
- MRI is still the gold standard for distinguishing borderline metastases. MRI has a particularly important role in the detection and assessment of bony secondary tumours.

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:³⁴

- Low risk (T1c/T2a; Gleason grade ≤ 6 ; PSA concentration ≤ 10 ng/ml)
- Intermediate risk (T2b; 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 brachytherapy
- Neoadjuvant/adjuvant hormone therapy
- Novel therapies

There is no consistent evidence for superiority of any of the three main radical treatments: radical prostatectomy, EBRT or brachytherapy.

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 or repeat biopsy 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 100% prostate cancer-specific survival at 10 years is achievable.^{35, 36}
- Active surveillance should be distinguished from watchful waiting. Traditional watchful waiting involves relatively lax 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-risk, clinically localised prostate cancer
 - Clinical stage T1c/2a
 - Gleason grade $\leq 3+4$
 - PSA concentration <15 ng/ml
 - Positive biopsies $\leq 50\%$
 - 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 and who have cancer in $<50\%$ of their total number of biopsy cores with <10 mm of any core involved.²⁹

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.³⁷ 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.³⁶ All patients had low-risk disease with PSA <10 ng/ml, PSA density <0.2 ng/ml per ml, stage T1c/T2, Gleason score $\leq 3+3=6$, 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.

- Van As et al. reported the outcome of 326 men recruited to the Royal Marsden active surveillance study from 2002 to 2006, at a median follow-up of 22 months.³⁵ Median age was 67 years, and median initial PSA concentration 6.4 ng/ml. Sixty-five patients (20%) had deferred radical treatment, 16 (5%) changed to watchful waiting because of increasing co-morbidity, 7 (2%) died of other causes, and 238 (73%) remain on surveillance. There were no deaths from prostate cancer and no men had developed metastatic disease.
- It is possible that targeted radical treatment, based on an active surveillance strategy, will be as effective, and considerably less morbid, than radical treatment for all cases. The ProSTART phase III trial will compare the long term outcomes of active surveillance with those of immediate radical treatment, and aims to recruit approximately 2100 patients.

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. Patients who eventually develop symptoms of progressive prostate cancer receive palliative treatment, usually with hormone therapy.
- Watchful waiting is particularly suitable for patients aged over 75 years or younger men with significant co-morbidities.
- Watchful waiting should be distinguished from active surveillance. Conventional watchful waiting involves relatively lax 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 progression.

Patient selection

- Asymptomatic clinically localised prostate cancer
 - Clinical stage T1–3
 - 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:²⁹
 - Men with localised prostate cancer who have chosen a watchful waiting regimen and who have evidence of significant disease progression (that is, rapidly rising PSA level or bone pain) should be reviewed by a member of the urological cancer MDT.

Radical treatments

Radical prostatectomy

There are now four approaches to performing a radical prostatectomy: retropubic, perineal, laparoscopic and robotic. The procedure involves removal of the whole prostate and the seminal vesicles. The most commonly used approaches are retropubic and perineal, but laparoscopic and robotic techniques are becoming more frequently adopted. The newer approaches have the advantage of reduced blood loss and shorter inpatient stays.

Overview

- In 1997, 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%.³⁸

Patient selection

- Anaesthetic fitness
- At least 10 years' life expectancy
- Complications increase and benefits decrease in patients aged >70 years

Side-effects of treatment

- Based on the systematic review by Selley et al., the following side-effects should be considered:³⁸
 - Operative and post-operative mortality: 0.2–1.2%
 - Sexual dysfunction: 51–61%
 - Incontinence (mild stress): 4–21%
 - Incontinence (total): 0–7%

Clinical evidence

- One randomised trial has compared radical prostatectomy with watchful waiting in localised prostate cancer.³⁹
 - The trial randomised 695 men with localised disease between radical prostatectomy and watchful waiting.
 - At a median follow-up of 8.2 years, randomisation to radical prostatectomy was associated with a benefit both in terms of disease-specific mortality (hazard ratio [HR] 0.56; 95% confidence interval [CI]: 0.36–0.88; p=0.01) and overall mortality (HR 0.74; 95%CI: 0.56–0.99; p=0.04).
 - This translated into 10-year OS of 73% versus 68% (p=0.04) for radical prostatectomy versus watchful waiting.
 - In terms of 10-year freedom from distant metastases, the absolute benefit of surgery versus watchful waiting was 10% (84.8% versus 74.6%; p=0.004).
 - However, patients need to weigh these benefits against the risk of adverse consequences of treatment. The 5% absolute improvement in 10-year survival was achieved at the expense of a 35% absolute increase in the risk of erectile dysfunction and a 28% absolute increase in the risk of urinary leakage.

- Faced with these figures, some patients would choose surgery, but many would choose conservative management.⁴⁰
- The above findings are now updated to incorporate a further 3 years of follow up. At 12 years:⁴¹
 - 12.5% of the surgery group and 17.9% of the watchful waiting group had died of prostate cancer (difference = 5.4%, 95%CI: 0.2–11.1).
 - 19.3% of men in the surgery group and 26% of men in the watchful waiting group had been diagnosed with distant metastases (difference = 6.7%, 95%CI: 0.2–13.2).
 - This follow-up analysis was consistent with the previous findings. Radical prostatectomy can reduce prostate cancer mortality and risk of metastases but no further benefits were seen beyond 10 years of follow up in this study.

Neoadjuvant and adjuvant hormone therapy with radical prostatectomy

- At present, 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.^{42–45}
- Similarly, there is currently no evidence that adjuvant hormone therapy provides a survival advantage for patients with pathologically proven localised disease.^{46, 47}

Adjuvant radiotherapy after radical prostatectomy

- The EORTC 22911 study was designed to investigate benefit for immediate postoperative radiotherapy in 502 patients with pT3 disease or positive surgical margins as opposed to radiotherapy offered for biochemical or clinical relapse.⁴⁸
 - After a median follow up of 5 years, biochemical progression-free survival (PFS) was significantly improved in the immediate radiotherapy group (74.0% versus 52.6%; $p < 0.0001$). Clinical PFS was also significantly improved ($p = 0.0009$) and the cumulative rate of locoregional failure was significantly lower ($p < 0.0001$), both in favour of the group treated with immediate radiotherapy. There was no significant difference for OS (in the region of 92% for both groups at 5 years).
 - In terms of toxicity, at 5 years the cumulative incidence of events of grade three toxicity was 2.6% in the wait and see group and 4.2% in the immediate radiotherapy group ($p = 0.0726$). No grade 4 events were recorded.
- 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.⁴⁹
 - There was again a statistically significant improvement in biochemical control (HR 0.43; 95%CI: 0.31–0.58; $p < 0.001$) for the group treated with immediate adjuvant radiotherapy. This study had a longer median follow-up at the time of analysis of 10.6 years and adjuvant radiotherapy was associated with a trend towards better metastasis-free survival (HR 0.75; 95%CI: 0.55–1.02; $p = 0.06$), and OS (HR 0.80; 95%CI: 0.58–1.09; $p = 0.16$).
 - Proctitis (3.3% versus 0%), urethral stricture (17.8% versus 9.5%) and urinary incontinence (6.5% versus 2.8%) were seen more often in the adjuvant radiotherapy arm.
- The RADICALS study is investigating the timing of radiotherapy (immediate versus early salvage) and hormone duration.⁵⁰

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%.³⁸
- 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.⁵¹
- 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 65–70 Gy. 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 proctitis⁵² and has allowed for dose escalation to the whole prostate to 78 Gy.

Intensity Modulated Radiotherapy (IMRT)

- IMRT is an advanced technique of 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. IMRT is currently under evaluation, particularly for the irradiation of pelvic lymph nodes.
- IMRT may result in reduced rectal toxicity when using doses greater than 80 Gy.

Dose escalation

- 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.⁵³
 - 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.⁵⁴
 - 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.
 - Although these and other studies have shown benefits from dose escalation with 3D-CRT techniques, 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.⁵⁵
 - 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 \geq grade 2 gastrointestinal toxicity at 4%.⁵⁶
- 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.⁵⁷
- 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.⁵⁸

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.

EBRT plus neoadjuvant hormone therapy

- Neoadjuvant hormone therapy reduces prostate volume by 30–40%.^{59, 60} This can reduce the size of the treatment field 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).⁶¹
- 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.⁶²

- 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%, $p=0.015$).⁶²
- 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.⁶³

EBRT plus adjuvant hormone therapy

- 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.⁶⁴
 - 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.⁶⁵
 - 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 ($p=0.04$).

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.⁶⁶
- 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.⁶⁷
- In intermediate-risk localised disease, the comparison is less clear, because many studies have added EBRT in combination.⁶⁸
- Brachytherapy is a single-step 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 ($p=0.0003$).⁶⁹

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.⁷⁰

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:⁶⁷
 - Irritant urinary symptoms: 46–54%
 - Acute urinary retention: 1–14%
 - Acute proctitis: 1–2%
 - Chronic adverse events (reinforced by Wills et al., 1999⁷¹):
 - Incontinence: 5–6%
 - Haematuria: 1–2%
 - Strictures: 1–2%
 - Proctitis: 1–3%
 - Erectile dysfunction: 4–14% (or up to 38% in Wills et al., 1999⁷¹ and up to 50% at 5 years in Merrick et al., 2001⁶⁸).

Clinical evidence

Table 4: Experience using trans-perineal implants as monotherapy (T1, T2 cancers)

Author	Number of men	Isotope	Median follow-up (months)	PSA results (months)
Beyer & Priestley, 1997 ⁷²	489	I-125	35	79% with PSA <4.0 ng/ml (5 years)
Blasko et al., 1995 ^{73*}	197	I-125	36	93% progression-free (5 years)
Wallner et al., 1994 ⁷⁴	62	I-125	19	83% progression-free (2 years)
Stock et al., 1996 ⁷⁵	97	I-125, Pd103	18	76% progression-free (2 years)

*Series excluded Gleason grade >7, 38% with pre-treatment PSA ≤4.0 ng/ml

- Beyer et al. compared failure-free survival following brachytherapy alone with EBRT. Brachytherapy was shown to be equal to EBRT in those with low-risk disease (T1c, T2a, Gleason grade ≤6, PSA ≤10 ng/ml), but there were poorer outcomes in those with higher-risk disease.⁷⁶
- Merrick et al. carried out a literature review comparing brachytherapy with radical prostatectomy and EBRT in clinically localised prostate cancer. For low-risk disease, biochemical results for brachytherapy were similar to radical prostatectomy or EBRT. For intermediate- to high-risk disease, those treated with brachytherapy +/- EBRT had a more durable biochemical outcome.⁶⁸
- Ragde et al. studied modern prostate brachytherapy using PSA results in 219 patients with up to 12 years of observational follow-up. The 10-year DFS after I-125 was 66% in those with low-risk disease and 79% in those with high-risk disease after brachytherapy and EBRT.⁷⁷
- 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.⁷⁸

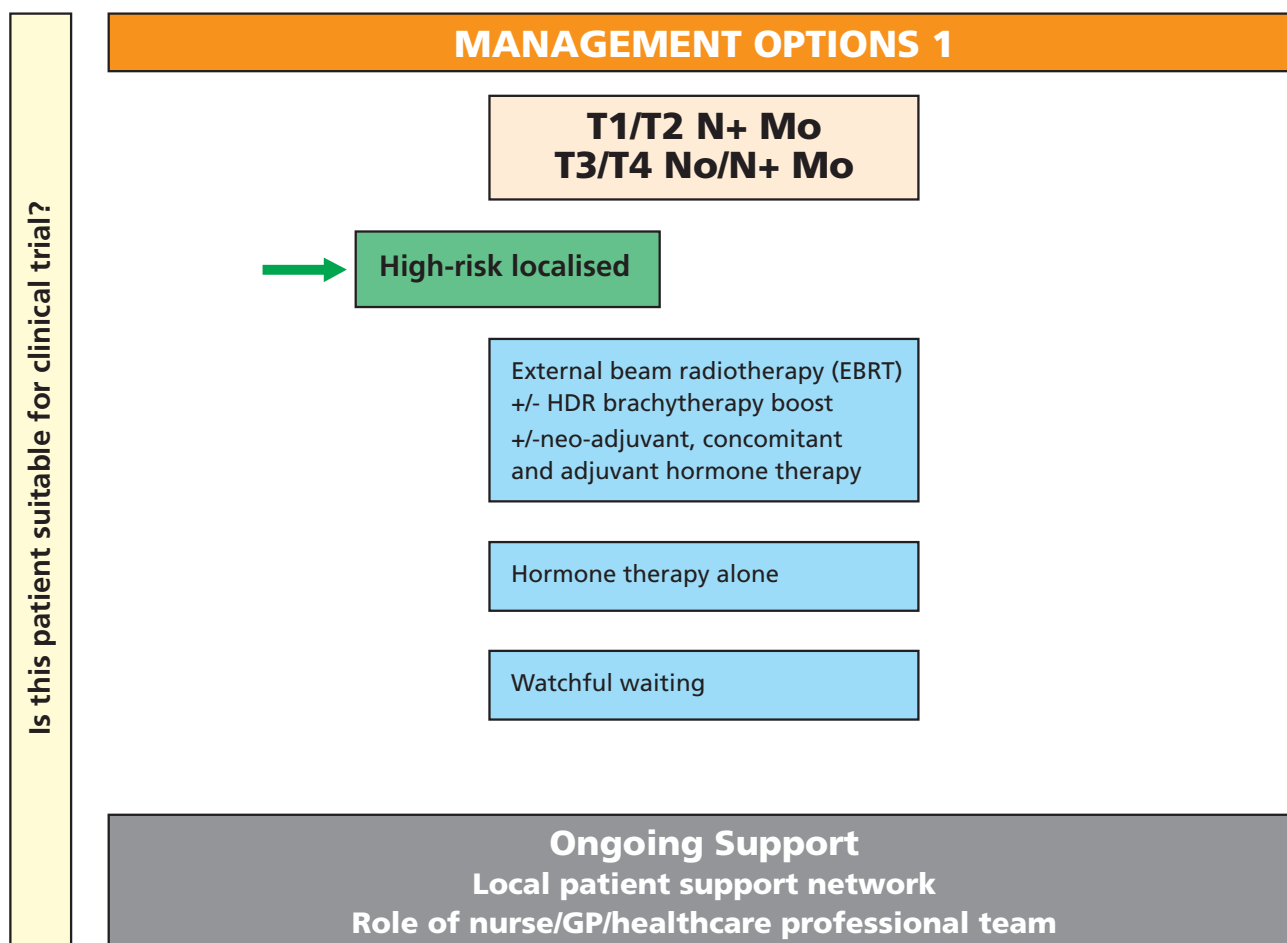
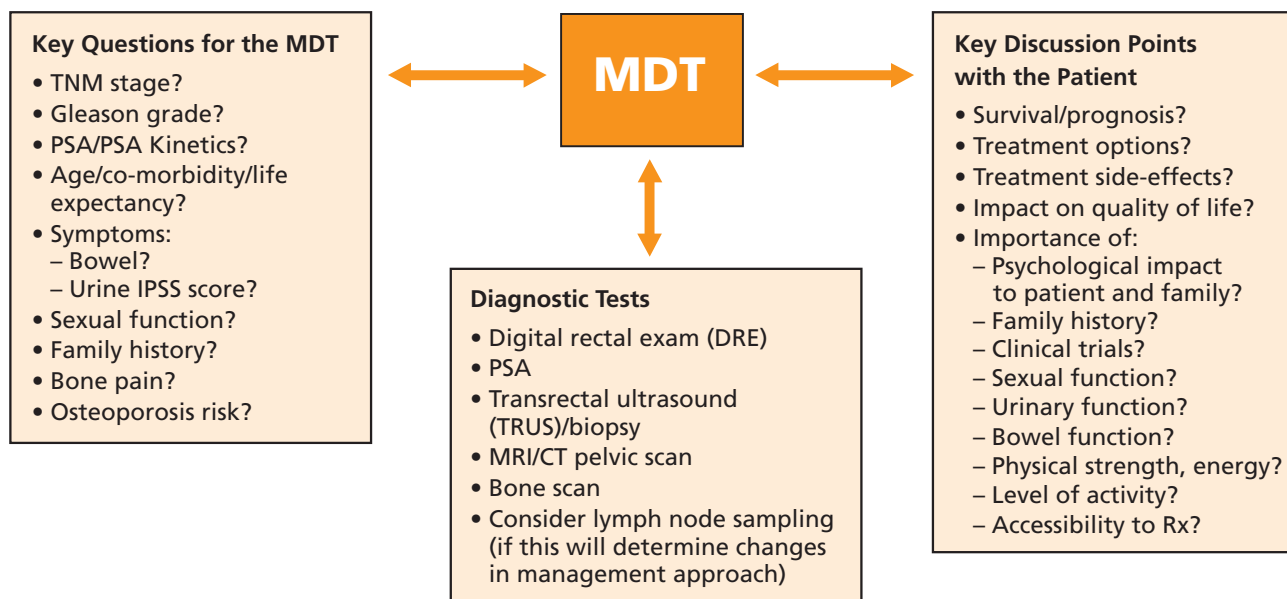
Novel therapies

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
 - Early results established the low incidence of serious side-effects and good PSA control^{79, 80}
 - 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
- 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 setting²⁹
 - After further clarification, it was agreed that these treatments would be funded by Primary Care Trusts provided patient data were collected in an approved way. Following consultation with the BAUS section of Oncology, a national database has been established to collect data from prostate cancer patients undergoing cryotherapy or HIFU for prostate cancer. Inclusion of patients in this database is considered necessary to fulfil the NICE guidelines.
- These treatments may be offered to patients with stage T1, T2 or T3 as a primary treatment or in salvage prostate cancer patients.
 - The staging requirements are a positive biopsy and MRI and bone scan showing no evidence of metastatic spread.

Locally Advanced Disease (Non-metastatic): Management Options

Figure 3: Treatment algorithm for locally advanced (non-metastatic) 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

Overview

- Data on the use of watchful waiting in locally advanced disease is sparse.
- Two non-randomised studies concluded that immediate orchidectomy was not associated with a survival advantage compared with therapy delayed until metastatic progression.^{81, 82}
- 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.⁸³

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.⁸⁴

Hormone therapy

Immediate versus deferred hormonal treatment

- 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.⁸⁵
 - 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 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.⁸⁶

Table 5: Effect of immediate versus deferred hormonal treatment⁸⁵

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

Hormone therapy plus standard care

- 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). 8113 patients with localised or locally advanced non-metastatic prostate cancer were included.⁸⁷
 - Objective PFS and OS were defined as the primary endpoints. At a third analysis, the median follow-up was 7.4 years. Exploratory analyses were also conducted to determine the efficacy of bicalutamide in clinically relevant subgroups.
 - A trend towards increased survival was seen for the subgroup treated with bicalutamide who would otherwise have undergone watchful waiting (HR 0.81; 95%CI: 0.66–1.01; p=0.06).
 - A significant improvement in objective PFS in favour of bicalutamide 150 mg for all locally advanced disease patients was demonstrated irrespective of standard care received (HR 0.69; 95%CI: 0.58–0.83; p<0.001). For the watchful waiting group this was (HR 0.60; 95%CI: 0.49–0.73; p<0.0001). However, there was no difference in OS between the two groups.

Radiotherapy plus 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.⁸⁸
 - 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.

Side-effects

- Luteinising hormone releasing hormone (LHRH) agonists: side-effects include erectile dysfunction and loss of libido, reduction in bone mineral density, hot flushes and sweating, and weight gain.
- Bicalutamide (anti-androgens): side-effects include gynaecomastia and breast tenderness.
 - Mild to moderate gynaecomastia and breast pain are the most common adverse events described.⁸⁷

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 rapidly being 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). These uncertainties are compounded by the availability of new approaches to the delivery of radiotherapy, such as IMRT. The latter is intended to shape the radiation field more precisely to the tumour volume, thereby reducing the side-effects of treatment and possibly allowing dose escalation that enhances its local efficacy.

Radiotherapy target volume/lymph nodes

- In high-risk patients the consensus is that the seminal vesicles should be included.
- The RTOG 9413 trial was designed to determine whether there was an advantage in terms of PFS with total androgen suppression, whole pelvic radiotherapy followed by a prostate boost compared with total androgen suppression 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.⁸⁹
 - 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.

Radiotherapy 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.

- Evidence of the benefits of dose escalation has been demonstrated for T1–T3 prostate cancer by Pollack in a phase III randomised study at the MD Anderson Hospital.⁵³
 - 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 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).
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- These results confirmed the advantage of dose escalated radiotherapy with doses of over 80 Gy. IMRT has the potential to reduce late rectal toxicity as shown in a further study by Zelefsky which reports 3-year actuarial ≥ grade 2 gastrointestinal toxicity at 4%.⁵⁶
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- The CHHiP 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.⁵⁸

HDR brachytherapy boost

- HDR brachytherapy 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 used in combination with EBRT and is felt appropriate for patients with high-risk localised or locally advanced prostate cancer.⁹⁰

EBRT plus neoadjuvant hormone therapy

- Neoadjuvant hormone therapy reduces prostate volume by 30–40%.^{59, 60} This can reduce the size of the treatment field 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).⁶¹
- 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 250mg 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.⁶²
 - 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%, $p=0.015$).⁶²
 - 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 ($p=0.12$).⁶³
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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.

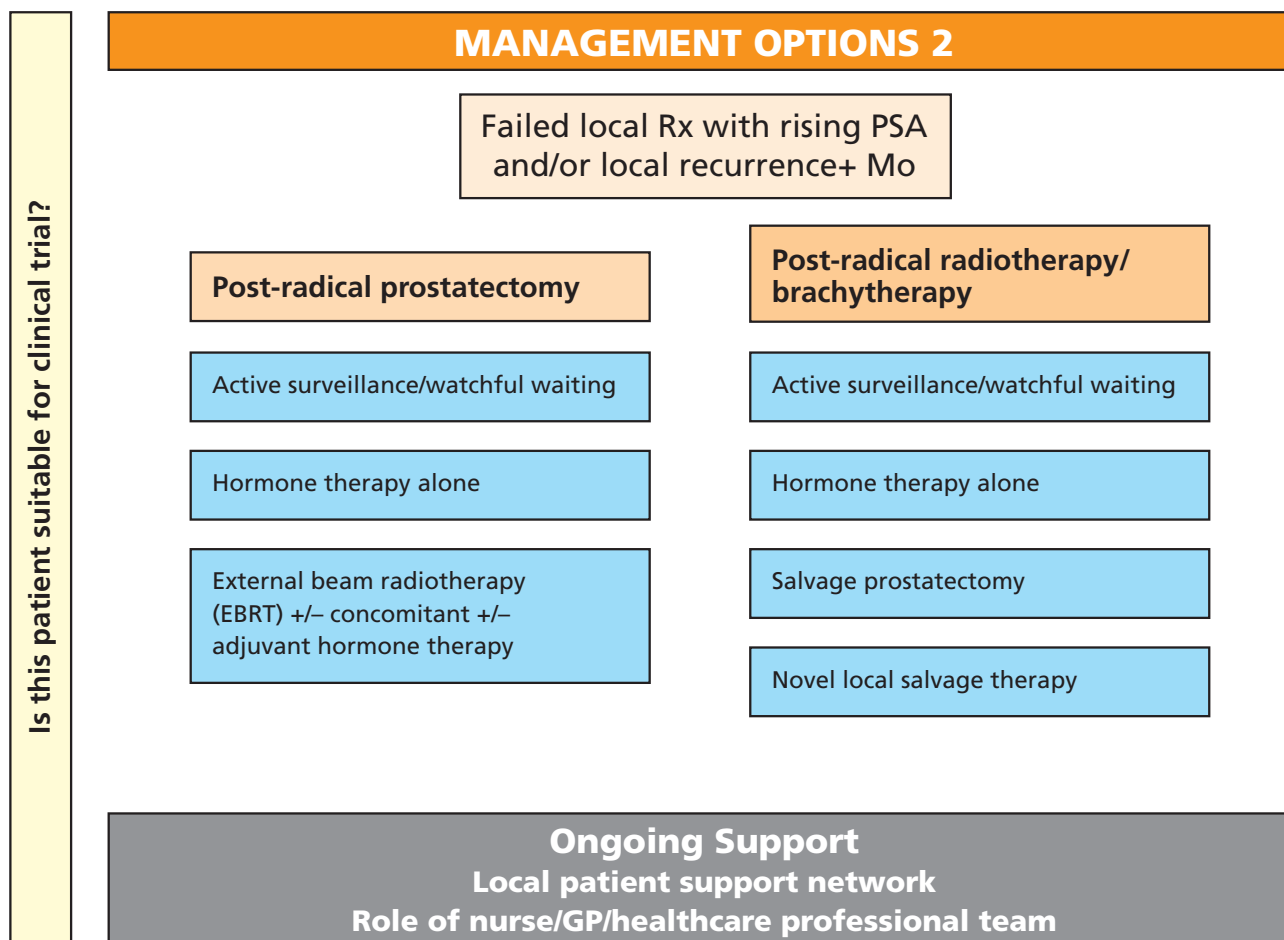
Clinical evidence

- 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 non-metastatic 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).⁹¹
 - After a mean follow-up of 66 months, the 5-year DFS rate was 74% versus 40% for the combined and EBRT alone groups, respectively (p=0.001).
 - Furthermore, the corresponding OS and cancer-specific survival rates at 5 years were 78% and 62% (p=0.0002), while the cancer-specific survival rates were 94% versus 79%.
 - A further analysis of this study with a median follow-up of 9.1 years reported 192 deaths (112 in radiotherapy alone and 80 in the combined treatment arm).⁹²
 - The addition of 3 years of ADT increased the 10-year OS from 39.8% to 58.1% (HR 0.60; 95%CI: 0.45–0.80; p=0.0004), clinical PFS from 22.7% to 47.7% (HR 0.42; 95%CI: 0.33–0.55; p<0.0001) distant PFS from 30.2% to 51% (HR 0.5; 95%CI: 0.38–0.65; p<0.0001) and clinical survival or PFS 17.6 to 37.0% (HR 0.43; 95%CI: 0.30–0.60; p<0.0001).
 - The 10-year cumulative index of prostate cancer mortality was 31% on radiotherapy and 11.1% on radiotherapy plus hormone therapy (HR 0.38; 95%CI: 0.24–0.60; p<0.001).
 - The 10-year cumulative index of cardiovascular mortality amounts respectively to 11.1% and 8.2% (HR 1.11; 95%CI: 0.59–2.09; p=0.75).
- 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).⁹³
 - 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).
- 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).⁹⁴
- A total of 945 patients remained analysable: 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.

- Hanks et al. (RTOG 92-02) investigated the use of long-term androgen suppression following neoadjuvant hormonal cytorreduction and radiotherapy in locally advanced prostate cancer (T2c to T4 with no extra pelvic lymph node involvement and PSA <150 ng/ml).⁹⁵
- 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 a median follow-up of 4.8 years, there was a significant improvement in 5-year DFS with combined adjuvant and neoadjuvant hormone therapy treatment compared with neoadjuvant treatment alone in patients with locally advanced prostate cancer (46% versus 28%; $p < 0.0001$).
- Further results from this study have been reported with a median follow-up of all surviving patients of 11.31 and 11.27 years for the two arms.⁹⁶
- 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%; $p \leq 0.0001$) 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 7.4 years at the third analysis. The primary endpoints were objective PFS and OS.⁸⁷
 - In locally advanced disease differences were seen between the standard care subgroups. For men receiving radiotherapy there was a significant improvement in OS with addition of bicalutamide (HR 0.65; 95%CI: 0.44–0.95; $p = 0.03$).
 - A significant improvement in objective PFS in favour of bicalutamide 150 mg for all locally advanced patients was demonstrated irrespective of standard care received (HR 0.69; 95%CI: 0.58–0.82; $P < 0.001$). This benefit was greatest for those receiving radiotherapy (HR 0.56; 95%CI: 0.40–0.78; $p < 0.001$).

Locally Advanced (Non-metastatic) Disease: Relapse after Primary Treatment

Figure 3: Treatment algorithm for locally advanced (non-metastatic) disease (cont.)



Rising PSA levels

- The PSA concentration at which to define treatment failure after prostatectomy varies in the literature.

Definitions of recurrence

- The Phoenix definition of relapse after radiotherapy is nadir plus 2.⁹⁷
- 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 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.⁹⁸ 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 unhelpful as this will always be negative, so there is no way of defining local versus distant disease categorically. Other factors that may aid this distinction include:
 - Timing and pattern of PSA relapse (rapid rise post-operatively indicates 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.⁵⁰

Clinical evidence

- The EORTC 22911 study was designed to investigate benefit for immediate post-operative radiotherapy in 502 patients with pT3 disease or positive surgical margins as opposed to radiotherapy offered for biochemical or clinical relapse.⁴⁸
 - After a median follow-up of 5 years, biochemical PFS was significantly improved in the immediate radiotherapy group (74.0% versus 52.6%; $p < 0.0001$). Clinical PFS was also significantly improved ($p = 0.0009$) and the cumulative rate of locoregional failure was significantly lower ($p < 0.0001$) both in favour of the group treated with immediate radiotherapy.
 - There was no significant difference for OS (in the region of 92% for both groups at 5 years).
 - In terms of toxicity, at 5 years the cumulative incidence of events of grade 3 toxicity was 2.6% in the wait and see group and 4.2% in the immediate radiotherapy group ($p = 0.0726$). No grade 4 events were recorded.
- SWOG 8794 has also 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.⁴⁹
 - There was again a statistically significant improvement in biochemical control (HR 0.43; 95%CI: 0.31–0.58; $p < 0.001$) for the group treated with immediate adjuvant radiotherapy.
 - This study had a longer median follow-up at the time of analysis of 10.6 years and adjuvant radiotherapy was associated with a trend towards better metastasis-free survival (HR 0.75; 95%CI: 0.55–1.02; $p = 0.06$), and OS (HR 0.80; 95%CI: 0.58–1.09; $p = 0.16$).
 - Proctitis (3.3% versus 0%), urethral stricture (17.8% versus 9.5%) and urinary incontinence (6.5% versus 2.8%) were seen more often in the adjuvant radiotherapy arm.
- The ECOG 7887 trial compared adjuvant ADT after radical prostatectomy and deferred hormonal therapy in patients with nodal metastases. 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.⁹⁹
 - 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; $p = 0.04$).
- Both SWOG 8794 and EORTC 22911 utilised late salvage treatment. It has been argued that early salvage treatment at the first sign of biochemical relapse could replicate the outcomes of adjuvant treatment and avoid treating some patients.
- This issue of the optimal therapy for patients with high-risk features after radical prostatectomy is being addressed the RADICALS study.⁵⁰
 - This multicentre phase III trial is investigating at the timing of post-operative radiotherapy with a comparison between adjuvant radiotherapy and observation with early salvage radiation for biochemical failure.
 - RADICALS includes a further randomisation to investigate the addition and duration of concomitant hormone therapy which remains another unanswered question in the post-operative setting.

Recurrence after radical radiotherapy

Overview

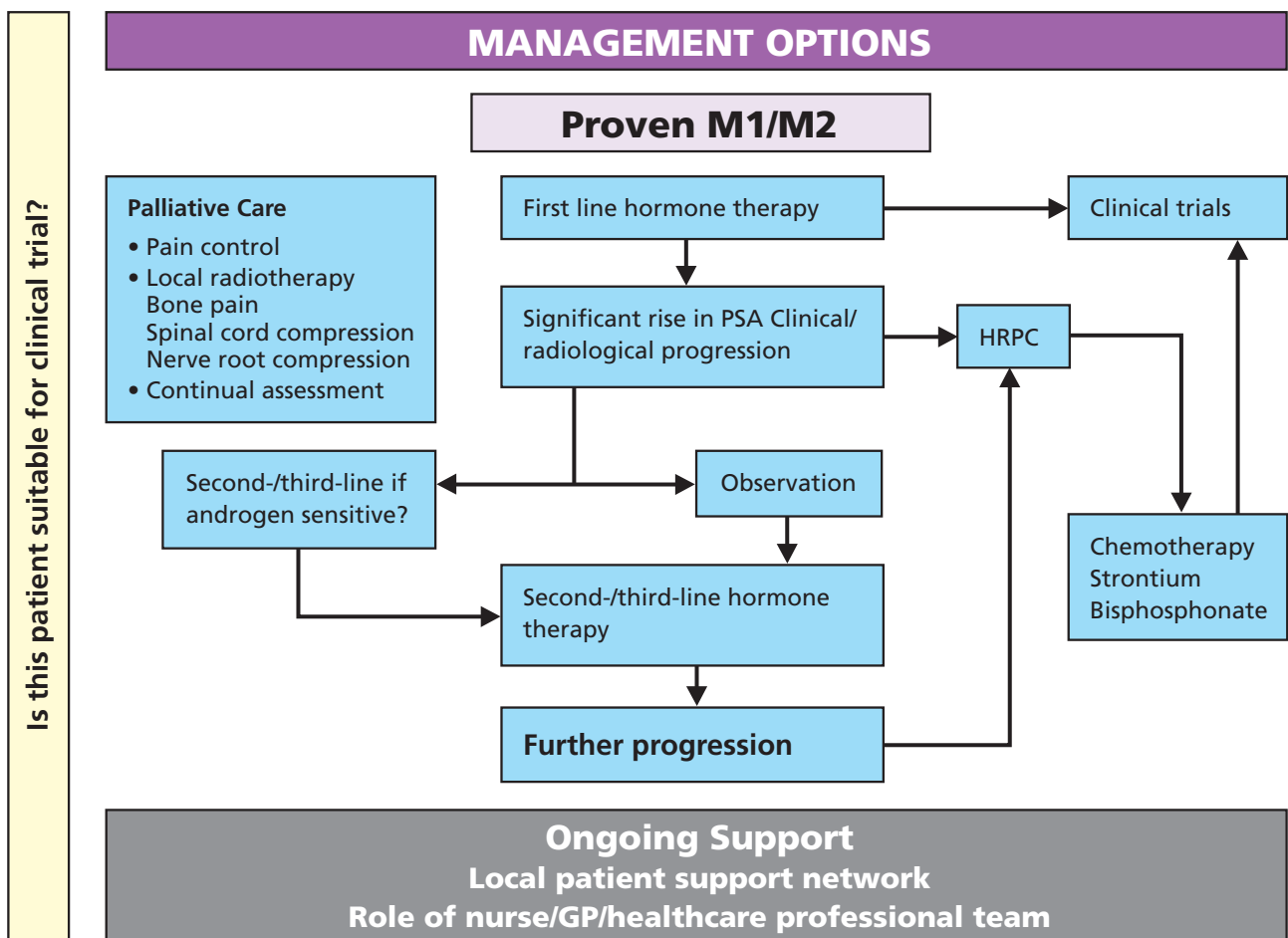
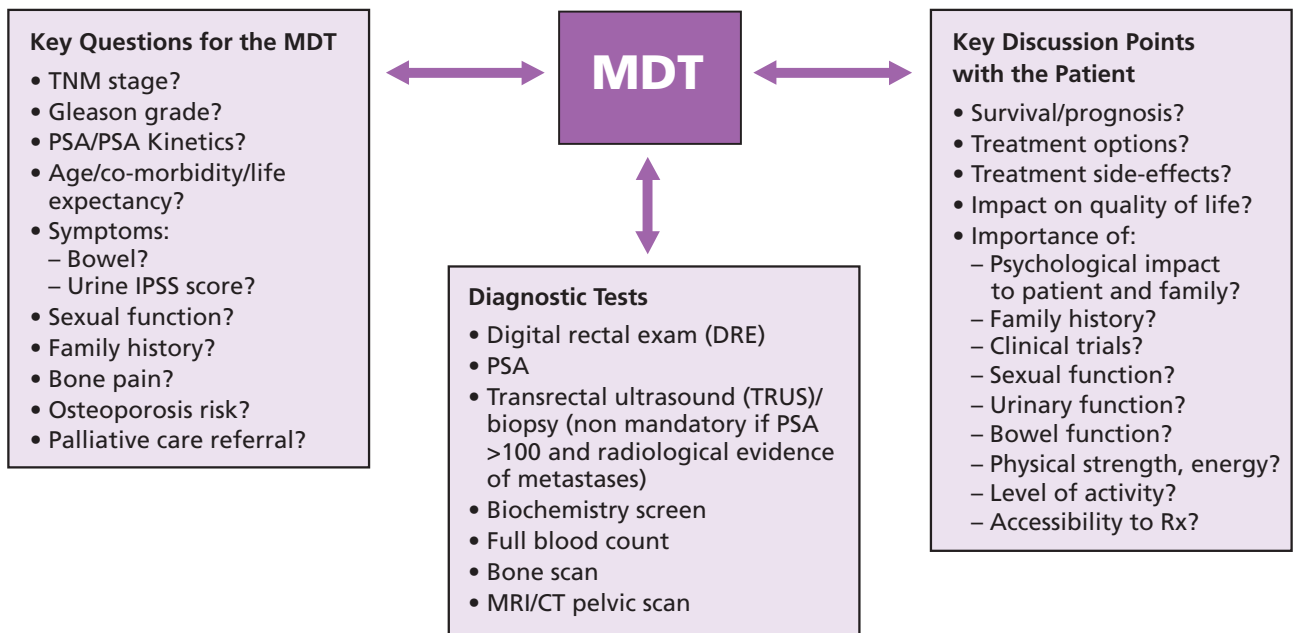
- The therapeutic options for recurrence following radiotherapy include:
 - Salvage radical prostatectomy: associated with 5-year biochemical DFS rates of 55–69%, but the technique is associated with a significant incidence of complications, such as rectal injury, anastomotic stricture and urinary incontinence.
 - 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

- Touma et al. reviewed the efficacy and safety of salvage radical prostatectomy, cryotherapy and brachytherapy for recurrence following definitive radiotherapy.¹⁰⁰
 - Salvage radical prostatectomy is 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, anastomotic stricture and urinary incontinence.
 - 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 one trial of 49 patients reported by Grado et al., complications included lower urinary tract symptoms, especially in the first 3 months. TURP was necessary in 14% of patients due to bladder outlet obstruction, while haematuria occurred in 4% of cases, stricture in 6%, rectal ulcers in 4% and rectal bleeding necessitating colostomy in 2%.¹⁰¹
- In 71 patients with localised disease following EBRT, following HIFU, 80% demonstrated negative biopsies and 61% had a nadir PSA concentration <0.5 ng/ml.¹⁰²
 - 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.

Advanced Prostate Cancer (Metastatic): Management Options

Figure 4: Treatment algorithm for advanced (metastatic) disease



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

Primary hormone therapy

Overview

- ADT is standard first-line treatment for the management of patients with metastatic disease. ADT can involve orchidectomy, LHRH agonists, anti-androgens and gonadotrophin-releasing hormone (GnRH) antagonists.
- Orchidectomy remains the gold-standard ADT against which all other treatments are compared because of its rapid effects on total testosterone concentrations.¹⁰³
- Survival appears equivalent with LHRH agonists and orchidectomy.^{104, 105}
- A meta-analysis has indicated that 2-year survival may be worse with medical treatment than with orchidectomy.¹⁰⁶
- Patients, however, prefer medical treatment and in terms of usage, drug treatment represents the standard of care at all disease stages.¹⁰⁷⁻¹⁰⁹
- GnRH antagonists are clinically equivalent to LHRH agonists without causing the initial testosterone surge seen with LHRH agonists. 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; $p < 0.001$).¹¹⁰
 - 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.

Immediate versus deferred hormonal treatment

- 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.⁸⁵
 - 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.⁸⁶

Table 6: Effect of immediate versus deferred hormonal treatment⁸⁵

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

Combined (maximum) androgen blockade

- 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.^{111, 112}
 - 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 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:¹¹¹
 - 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.

Second- or third-line hormone therapy

- Some patients will respond to second-line hormone therapy (CAB with the addition of an anti-androgen, anti-androgen withdrawal, diethylstilboestrol [DES]). 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 $\geq 50\%$ in 21% (16% to 27%) of 210 men with progressive prostate cancer who discontinued the anti-androgen component of their CAB therapy.¹¹³
 - 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.
- 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.¹¹⁴
- 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.¹¹⁵
- 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.¹¹⁶
- High-dose ketoconazole plus hydrocortisone has an approximate 30% response rate.¹¹⁷
- New agents such as abiraterone acetate, which inhibits non-testicular testosterone production and MDV3100, a potent anti-androgen, have been reported to obtain significant responses and are currently under evaluation.

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).
- 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.
- Oestrogens will commonly cause gynaecomastia and impotence, together with nausea, fluid retention, and venous and arterial thrombosis.
- Corticosteroid toxicity is dose-dependent, but includes diabetes, osteoporosis, mental disturbances and cushingoid features.

Chemotherapy, Strontium and Bisphosphonates

Those patients who do not respond to hormone therapy are considered to have hormone-refractory prostate cancer (HRPC; i.e. unresponsive to all hormone therapies) or castrate-refractory prostate cancer (unresponsive to treatment with LHRH agonists) and are candidates for chemotherapy, novel therapies and/or symptomatic local treatments.

Chemotherapy

- 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.¹¹⁶
 - 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.¹¹⁸
 - 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.¹¹⁹
 - 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.

Side-effects

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

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 phosphatase.¹²⁰
- Strontium is not associated with improvements in OS.¹²¹
- Four randomised clinical trials have reviewed the use of strontium.¹²²
 - 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.¹²³

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.

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.¹²⁴ 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 4mg 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).¹²⁵
 - 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:¹²⁴
 - 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).¹²⁶
 - 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).¹²⁷

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.¹²⁸
 - 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.
 - 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; $p=0.1$).¹²⁹
 - 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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