GUIDELINES FOR THE MANAGEMENT
OF UROLOGICAL CANCER

Prostate Cancer

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Introduction

The purpose of this manual is to provide a working manual for the management of prostate cancer within the West Anglia Cancer Network. It should act as a summary guide for the management of patients with prostate cancer based on the available published evidence and should be regarded as a template for best practice. Its scope is to aid all health practitioners involved in the care of the patient from primary care and referral, through treatment to follow up.

As constant modifications are being made, these guidelines should only be used to give an indication of current management. They should not be used to treat patients without checking that changes have not been made.

It is expected that by formalising management strategies and refining quality objectives and outcome measures, the manual will ensure objective auditing of the medical management process involving patients with prostate cancer.

These guidelines have been endorsed by the West Anglia Cancer Network Urology Site Specific Group. They will be reviewed and updated on an annual basis or more frequently as required.
Incidence

Prostate cancer is rare before the age of 40, and the risk increases with age, with approximately 27,000 new cases and 10,000 deaths per annum in the UK, it is the second commonest cancer in men (CRC-Cancer Stats Monograph, 2004:55-62).

Since the introduction of testing for serum prostatic specific antigen (PSA) the reported incidence of prostate cancer had risen rapidly and this is most prominent in the relatively younger group of men between 55 - 70 years.

GP Referral

All patients should be referred to their local Urology Multi-Disciplinary Team. Patients diagnosed with prostate cancer within the West Anglia Cancer Network will initially be discussed at the local multi-disciplinary team meeting. The decisions reached at this meeting will be documented on appropriate forms. Patients should receive treatment and care that are consistent with the agreed West Anglia Cancer Network prostate guidelines. Further developments in line with the NICE Guidance Document will be included in due course.

Urgent; The guidelines published by the Department of Health give criteria for fast-track referral (2 week rule):

- An elevated age specific PSA in men with a 10 year life expectancy
- Abnormal prostate on digital rectal examination (PSA will have usually been undertaken)

Routine; All other patients e.g.
- Significant prostatic symptoms with normal PSA

Investigations

PSA

Any patient <75 years with prostatic symptoms
Any patient with abnormal prostate on DRE

<table>
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<tr>
<th>Age</th>
<th>PSA micrograms/l Upper limit</th>
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<tr>
<td>40 – 49</td>
<td>2.5</td>
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<td>50 – 59</td>
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<td>60 – 69</td>
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<td>70 – 79</td>
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Notes

1. PSA can be used as sole diagnostic tool in elderly and unfit if DRE abnormal and PSA > 100 µg/l
2. In patients who had previously had TRUS and biopsy with negative histology, the use of % free PSA may inform the decision to repeat biopsies or not (ratio <25% more suggestive of Cancer)
TRUS + Biopsy of Prostate

- Any patient with PSA > age adjusted upper limit (ULN)
- Any patient with palpably abnormal prostate.
- Patients considered for radical prostatectomy may also undergo seminal vesicle biopsy.

Bone scintigram

- All Patients undergoing radical therapy (Clinician may feel not required if PSA < 10ug/ml and PSA <7).
- All patients with Gleason >= 7 disease
- Patients with symptoms of bone metastases.

MRI (or CT)

- Scans of Pelvis for radical radiotherapy
- Not possible to include diagnosis and planning in same scan.
- MRI is preferred to CT

Defining Tumour Stage and Grade

Pathology and tumour grade

The recommended histological grading system for adenocarcinomata is that described by Gleason (Gleason, et al. 1974) (see appendix one)

Tumour stage

In the UK the TNM is used (see 2002 edition in appendix 2) whereas in the USA Whitmore-Jewett system is popular.
Management options for early prostate cancer

For most patients there are will be a number of options available for the management of their early stage prostate cancer. As clinicians we should describe which treatment options are best suited to the patient's needs, along with their advantages and disadvantages. Patients, having been given detailed information, are encouraged to share in the decision making process. As there remains debate on the definitive treatment pathway, recruitment into clinical trials is also encouraged. The main management options include:

1. Monitoring alone – “active surveillance”
2. Hormone therapy alone
3. Radical prostatectomy
4. 3-D conformal external beam radiotherapy - EBRT
5. Radioactive seed implantation - brachytherapy

1. Monitoring alone

Type of patient who may be considered:

- Older frail patients or those with serious medical conditions
- Gleason sum 2-6 (well/moderately well differentiated) tumours
- T1/T2
- Asymptomatic
- Patient preference

The risk of progression is related to grade and stage. These risks should be explained to the patient. If the patient agrees he should be followed up initially at three monthly intervals with a PSA and rectal examination at each appointment. At a later stage once stability of the PSA reading has been established (over 2 years of active surveillance) the appointment interval may be increased to 6 monthly after discussion with the consultant in charge.

Monitoring should include a measure of PSA doubling time (PSAdt).

The patient should be managed according to the results of the PSA doubling time;

- PSAdt <10 months – intervention
- PSAdt >4 years – No intervention / continued surveillance
- PSAdt between 10 months and 4 years – consider treatment according to patient parameters (i.e. Radical or palliative treatment).

Charts exist to allow the risks to be explained to patients in a visual manner (Albertsen et al; JAMA 1998; 280:975-980).
Survival (white lower band) and cumulative mortality from prostate cancer (dark gray upper band) and other causes (light gray middle band) up to 15 years after diagnosis stratified by age at diagnosis and Gleason score. Percentage of men alive can be read from the left-hand scale, and percentage of men who have died from prostate cancer or from other causes during this interval can be read from the right-hand scale.
2. Long term androgen deprivation therapy alone

In the majority of men with more than a 10 year life-expectancy this option is unlikely to be appropriate as this strategy simply puts off the day when definitive therapy should be initiated, while adding to the overall morbidity of treatment. Patients who may reasonably be considered include:-

- Life expectancy less than 10 years.
- Significant urinary symptoms may increase the advantages of offering androgen deprivation.
- No other significant risk factor for osteoporosis
- Patient preference.

The options for androgen deprivation (see appendix for details) are:-

- LHRH agonists e.g. Goserelin
- Orchidectomy
- Anti-androgen monotherapy therapy eg. Bicalutamide, may be considered for selected patients in whom active therapy is indicated but potency or the side-effects of LHRH analogues are important issues.

3. Radical Prostatectomy

All patients require staging (at least with TRUS). Bone scan will be carried out if the tumour is of Gleason grade of 7 or more, or if the PSA is > 10. In most instances, either a pelvic MRI scan or CT abdomen and pelvis will be carried out. This treatment can be offered to the following men.

- Patients under 70 years with no other serious medical conditions.
- Life expectancy in excess of 10-15 years.
- T1/T2N0M0 and PSA < 15.
- Patient understands and accepts the risk of impotence or incontinence.
- Prostatectomy may be advantageous if there is a history of marked LUTS.
- Contraindication to EBRT or 125I-seed brachytherapy
- Patient preference.

4. 3-D conformal external beam radiotherapy - EBRT

For full details see appendix 4. Patients should be staged as outlined above.

- T1-3 N0 M0
- Any Gleason grade
- Life expectancy > 10 years if Gleason 2-6, and >5 years if Gleason 7-10
- No history of radio sensitivity or previous pelvic radiotherapy.
- Contraindications to brachytherapy or radical prostatectomy.
- Patient preference.
Radiotherapy and hormone therapy recommendations:

**a) Radical radiotherapy without associated hormone therapy**

- pT1a/pT1c (10% sample volume) and Gleason <7 and PSA in normal range
- Normal potency
- Patient preference

**b) Hormone cyto-reduction 3-6 months before and concurrent with radical radiotherapy**

- pT1b/c-clinical T2a/b/c
- Gleason < 8
- PSA ≤ 30

NB; Patients should be given the radiotherapy and hormone-cytoreduction fact sheet describing the likely and possible side effects of hormones – the patient should clearly understand that it is his responsibility to make an appointment with the GP for the next Depot injection (this fact should also be written on the advise sheet). The GP should receive a clear indication of the date of the next injection and the treatment duration - i.e. until the start of the radiotherapy then stop.

**c) Continuing hormones after radical radiotherapy (3 years)**

Patients at a higher risk of systemic disease may be considered for adjuvant hormone therapy for 3 years.

- Gleason 8 or above
- Clinical T3/4a
- Initial PSA > 30 (not in acute retention or with UTI)

(NB: The two trials showing a survival advantage in this setting, hormones were started at the completion of Radiotherapy. Other clinicians who use hormone cytoreduction prefer to monitor post radiotherapy PSA, symptoms and PR examination before deciding on long term adjuvant therapy)

**d) Indefinite Hormone Therapy Followed By Palliative Radiotherapy**

- N+ and/or M+ disease
- T4b
5. Radioactive seed implantation - Brachytherapy

Patients may be considered with the following factors:-

- Well or moderately differentiated tumours (Gleason < 7)
- No prior TURP
- PSA <15
- Prostate volume <50mls, no pubic arch interference
- Minimal lower urinary tract symptoms (LUTS)
- T1N0M0 or small volume T2N0M0
- Patient preference

At the present time eligible patients should be referred to Dr David Bottomley, Cookridge Hospital Leeds although a local facility is planned.

6. Radiotherapy after radical prostatectomy

Each case will be discussed at the MDT. Indications include a rising PSA post-operatively, or a PSA which fails to become unrecordable. Positive margins alone are not an indication for immediate post-operative radiotherapy unless the PSA begins to rise. Patients who do best are those with combined Gleason scores <8 and those whose PSA is < 1 microgram/dl at the time radiotherapy is initiated. The use of androgen deprivation in this setting is decided on an individual patient basis.

Patients should be warned that there is a risk of worsening urinary incontinence following radiotherapy in this setting.
Management options for locally advanced prostate cancer (without metastases)

Patients with T3b or T4 could be considered for radical or palliative radiotherapy plus hormone therapy (see radiotherapy section). These decisions should be made on an individual level with the help of the MDT. Other options include hormone therapy alone or even watch and wait in patients with other serious medical conditions. Prostatectomy or brachytherapy are not considered.
Management options for Metastatic Disease

The aims in this setting are local control and palliation. Local therapies for the prostate depend on the symptoms, extent of disease (locally and metastatic) and the performance status of the patient. Assessing the symptomatic response to hormone therapy is the usual course but palliative TURP or radiotherapy may well be appropriate (Prostatectomy or brachytherapy are not considered). Treatment of systemic disease depends on the existing therapies at the time of metastatic development and the individual circumstances of the patient. Examples of suggested pathways are demonstrated below:

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<tr>
<td>LHRH agonist or orchidectomy</td>
<td><strong>Next</strong> Add Antiandrogen (e.g. Bicalutamide 50mg od)</td>
<td><strong>Replace previous with</strong> Diethystilboestrol 1-3 mg po od and Aspirin 75mg od</td>
<td>Replace previous with Prednisolone 10 mg od</td>
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<td>LHRH agonist or orchidectomy <strong>AND</strong> Antiandrogen (e.g. Bicalutamide 50mg od)</td>
<td><strong>Next</strong> Withdraw Antiandrogen</td>
<td><strong>Replace previous with</strong> Diethystilboestrol 1-3 mg po od and Aspirin 75mg od</td>
<td>Replace previous with Prednisolone 10 mg od</td>
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<td>(also consider Mitoxantrone / Clinical Trials)</td>
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1 Ref: Clinical Oncology 2004;(16);505-516
2 Aspirin 75mg od has fewer side effects than Warfarin
3 In patients with a history of thromboembolic disease consider warfarin 1 mg od. Warfarin requires an INR test at 2 - 4 weeks - If this value is below 2 then it does not require measuring again.
Other Considerations

- LHRH agonist should be covered with anti-androgen for the first 3 weeks - Anti androgen therapy should be given for at least three days before the first injection of LHRH agonist, and continued for three weeks after the first injection (British National Formulary)
- Consider breast bud irradiation if long term bicalutamide or diethystilboestrol is planned.
- Any anti-androgen can be considered but Flutamide is not as well tolerated as Bicalutamide
- Megestrol acetate 40–80 mg qds can be an option although response rates very low
- Cyproterone acetate 10–50 mg od is useful to treat the hot flushes associated with LHRH analogue. As monotherapy there is a risk of liver damage and it is less effective than LHRH analogue.
- The use of Mitoxantrone is increasing and its use should be considered in cases of clinical progression on hormone therapy.
- Consider clinical trial if available

Chemotherapy in Prostate Cancer

In 2004 two large phase III randomized controlled trials both demonstrated a survival advantage for the use of docetaxel based chemotherapy in patients with advanced/metastatic prostate cancer when compared to mitoxantrone based chemotherapy. This treatment is currently unavailable within the WACN due to the current prohibitive cost of docetaxel. NICE guidance, expected in the new year, may change this situation. Currently therefore, mitoxantrone 12mg/m² (usually capped at 20mg total dose) with prednisolone 10mg po od every 3 weeks for up to 10 cycles is considered standard therapy after all appropriate hormone therapy has failed. This treatment has not been shown to have a survival advantage but produces useful palliation of symptoms in up to 50% of patients.

Small cell carcinoma.

This is a rare and often aggressive histological subtype of prostate cancer which may be present at diagnosis or may develop within and then outgrow an existing prostatic adenocarcinoma. Care should be taken to exclude a small cell tumour of the bladder with prostatic infiltration. The treatment of choice for patients with apparently localized disease is initial chemotherapy, for up to 6 cycles, with an approved small cell regime such as CAV (cyclophosphamide, doxorubicin, vincristine), ACE (doxorubicin, cyclophosphamide, etoposide) or EP (etoposide, cisplatin), followed by radiotherapy to the prostate to a dose of 55Gy/20 fractions over 4 weeks. For patients with metastatic disease at presentation chemotherapy alone is more appropriate unless there is concern regarding the risk of uncontrolled local progression when a palliative radiotherapy treatment schedule to the prostate can be offered.
Prostatic ductal carcinoma.

This is an aggressive tumour which should be managed along the lines of a transitional cell carcinoma. Fit patients with apparently localized disease should be offered radical radiotherapy (55Gy/20 fractions). For advanced disease consider chemotherapy with cisplatin/gemcitabine or MVAC.

Therapy for painful bone metastases

Local radiotherapy to the painful area is the treatment of choice. Usually an 8 Gy single fraction is recommended, although five fractions may be need when retreated. Other therapies include:-

- Strontium \(^{89}\) - currently not available in WACN
- Surgical decompression
- Internal fixation
- Bisphosphonates

Palliative treatment

This should be designed to improve quality of life. Patients should be given the least invasive procedures to minimise the occurrence of adverse side effects/complications of treatment. Early referral to the palliative care team should be made to ensure patients/users have access to specialised palliative care as and when required. Palliative care teams are available in all of the West Anglia Cancer Network organisations providing prostate cancer care.
Patient Information

All patients should be offered clear and comprehensive written information on

- Nature of the disease.
- Diagnostic procedures being undertaken.
- Treatment options available.
- Likely outcomes of treatment in terms of benefits, risks and side effects.
- Contact details for co-coordinator/specialist team.
- Advice on sexual issues, continence and fertility.

The network has endorsed the use of information leaflets provided by BACUP and these should be available for patient use

Other web resources include:

Cancernet UK - www.cancernet.co.uk
The Prostate help association – www.pha.u-net.co.uk.
The impotence association – www.impotence.org.uk.

Follow up

Following treatment patients should be given an appointment for review in the appropriate clinic Thereafter follow up will be 3 to 6 monthly for first year, 6 monthly year two – four and thereafter, all being well annual follow up.

Audit Programme

An audit programme for prostate cancer has been agreed by the West Anglia Cancer Network Urology Site Specific Group,
Appendices

Appendix 1  Prostate Histology, grading
Appendix 2  Staging of prostate cancer
Appendix 3  Advice for Hormone therapy
Appendix 4  Further Radiotherapy Details
Appendix 5  Clinical Trials supported by the network
Appendix 6  Spinal Cord Compression Patient Information Sheet
Appendix 7  IV Bisphosphonate Guidelines
Appendix 8  Osteoporosis Guidelines
Appendix 9  Radical Radiotherapy Post-Radical Prostatectomy
Appendix 1 - Histology

Prostate specimens should be handled in accordance with the latest version of the relevant Minimum Dataset published by the Royal College of Pathologists, available at www.rcpath.org. These guidelines are evidence based and specify minimum data set criteria for the specimen gross description and microscopic diagnosis sections of the pathology report. Comprehensive descriptions of gross and microscopic appearances of tumours and aids to diagnosis are available in standard surgical pathology texts. Key points on handling and reporting of prostate specimens are noted below.

Prostate Biopsies

Prostate core biopsies are usually received as samples from the right and left sides, or multiple site biopsies (eg sextant protocols). The number of core biopsies taken and the sites should be specified by the surgeon or nurse practitioner on the histology request form, with information on the PSA level and the clinical features.

In the laboratory, the cores should be counted and measured. This acts as a record of what is received and also serves to give a means of monitoring tissue loss and adequacy of sectioning when compared with the tissue represented on the slides. Limiting the number of biopsies per cassette reduces tissue loss when block trimming, but in most departments placing one biopsy per cassette is not a practical option. Where multiple biopsies are placed in a cassette, it is important that they are embedded as flat as possible to minimise tissue loss on sectioning. Possible options include placing biopsies on a surface (such as cellulose acetate) when fixing, to prevent distortion, or compressing the biopsies within the cassettes.

Whether serial sections or levels are taken depends on the laboratory preference, but in view of the small size of some tumours, it is important to ensure that the full length of all cores is represented on the sections.

Saving spare intervening sections for immunohistochemistry is helpful as it provides a direct comparison with the H&E stained sections. More than one section on the coated slide is helpful in assessing consistency of immunostaining in the glands in question. In many cases it is possible to diagnose carcinoma without the need for immunostains, but in doubtful or difficult cases or where the tumour focus is small, they may enable a definitive diagnosis to be made. Immunostains that demonstrate basal cells are helpful in distinguishing benign acinar proliferations (adenosis) or atrophic glands from malignancy or confirming that dysplastic glands represent high grade prostatic intra-epithelial neoplasia, rather than invasive tumour. Basal cells may be difficult to reliably identify on H&E stained sections, therefore a basal cell marker should be used to demonstrate them if there is any doubt about their presence. The diagnosis of carcinoma should not be based on an absence of basal cells alone, but should be made on a combination of this and architectural and cytological features of malignancy. All glands in any ‘suspect’ foci should be negative for basal cells for a diagnosis of carcinoma to be made.

The choice of basal cell marker will depend on laboratory preference and success with a particular technique. Commonly used stains are:

Positive stain for basal cell cytoplasm: CK5/6  34BE12  LP34
Positive stain for basal cell nuclei: P63

Alpha-methyl-CoA-racemase (AMACR, p504S) may also be used to positively stain carcinomatous glands and high grade prostatic intra-epithelial neoplasia (PIN), and may be particularly helpful in cases where there is a strong suspicion of carcinoma, but only a small number of malignant glands. When combined with a basal cell stain, a firm diagnosis may be possible.

Immunostains may also be required if a metastatic malignancy or direct involvement from another primary site is suspected from morphological features. Prostate specific antigen (PSA) and prostate specific acid phosphatase (PSAP) immunostains may help to confirm primary prostatic origin.

In line with current recommendations, only high grade PIN is mentioned in reports. In cases where there is a focus of atypical acini that is of uncertain significance, the degree of suspicion of carcinoma should be stated.

If there is prostatitis of a degree which might be responsible for a raised PSA level, this should be mentioned in the report, but minor degrees of inflammation are common and are not significant.

Microscopy report for prostate cancer

Useful information on histological assessment of prostate cancers and TMN staging is available in: WHO Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. IARC Press: Lyon 2004.

The following features should be specified in the microscopy report:

- **Type**
  The considerable majority of prostate cancers originate in the glandular component of the gland, (adenocarcinomas) mainly in the peripheral zone of the prostate. ‘Adenocarcinoma’ is the term used for ‘usual’, conventional or microacinar prostatic carcinoma. Variable features, such as ductal, mucinous or signet ring appearances should be mentioned, but the tumour cannot be typed as such on a small needle biopsy sample. Typing as one of these variants is done on radical prostatectomy specimens.

  **Primary transitional and squamous cell cancers** are very rarely described but usually they have directly spread from the bladder. Carcinoïd and small cell carcinomas may arise de novo or develop from prostate adenocarcinomas. These tumours may be chemo-sensitive but are highly malignant with a very poor prognosis. Sarcomas represent approximately 0.1% of prostatic malignancy: Rhabdomyosarcomas in younger patients; Leiomyosarcomas usually after 50 yrs. Secondary tumours of the prostate most commonly arise from direct infiltration from bladder cancers, but deposits from 1º tumours including malignant melanoma, bronchial carcinoma, non-Hodgkins lymphoma and acute leukaemia have been described.

- **Gleason Score**
  Grading systems have been shown to correlate with tumour stage, incidence of seminal vesicle and lymph node involvement, occurrence of distant metastases and
survival. However, the reproducibility of such systems is not perfect and there is considerable intra- and inter-pathologist variability (Gallee et al, 1990)

The histological grading system most commonly used is that described by Gleason (Gleason et al, 1974) and is given on adenocarcinoma and its variants. Unlike other grading systems, emphasis is placed on the assessment of the architectural growth pattern and degree of glandular differentiation, rather than cytological features, thus enabling grading to be performed at low or medium power magnification. Five tumour grades 1-5 are recognised (with sub-divisions to form 9 originally described patterns), forming a continuous spectrum of appearances from grade 1 being the well differentiated to grade 5, the most poorly differentiated. A simplified description of the histological appearances is given here:

**Gleason Grading of Prostate Cancer – summary of histological appearances:**
- Grade 1 Uniform closely packed separate glands forming a circumscribed nodule
- Grade 2 Slightly less uniform, separate glands, more loosely packed, with a partially circumscribed margin
- Grade 3 Single separate infiltrating often angulated glands (3A), very small infiltrating glands (3B) or circumscribed cribriform or papillary masses (3C)
- Grade 4 Fused raggedly infiltrating glands (4A), which may also consist of large pale cells ‘hypernephroid’ cells (4B)
- Grade 5 Solid rounded masses with necrosis (5A) or ragged infiltrating tumour (5B)

The majority of tumours do not have a uniform appearance, therefore the primary grade is assigned to the pattern which is predominant, and the secondary grade to the next most frequent. The Gleason score is the sum of the primary and secondary grades, unless only one tumour grade is represented, when the score is then simply the grade doubled. This gives a Gleason score range of 2-10. If a third less frequent grade is present, this is the tertiary grade and should be clearly reported if this is of higher grade than the primary and secondary grades. Modifications to the scoring system to incorporate higher grades into the Gleason score have been proposed for needle biopsy reports (eg Pan et al, 2000) because of the worse prognosis conferred by the presence of poorly differentiated elements. If a ‘modified’ method of Gleason score is used (i.e. including the tertiary higher grade element in the score), this should be clear from the text of the report. ‘Modified’ scores are not used in reporting radical prostatectomy specimens.

A Gleason grade should be assigned, even for small tumour foci. However, Gleason grading of tumours showing therapy related changes is not possible, unless sufficient areas can be identified within the tumour which do not show these artefacts.

Gleason scores of less than 5 are not usually made in assessing needle core biopsies, since entire tumour nodules are not represented in the fine cores. For biopsies from different sites, the Gleason scores at those sites should be stated.

- **Extent of tumour**
The number of cores involved by tumour should be stated. Additionally, some indication of extent of tissue involvement should be added, such as total tumour length, percentage of total tissue involvement or individual core measurements.

- **Other features**
If perineural invasion, extraprostatic tumour spread (tumour clearly within adipose tissue) or lymphovascular invasion are identified, these should be noted in the report. If seminal vesicle is present and invaded by tumour, this should be mentioned. The ejaculatory ducts may be lined by similar epithelium to the seminal vesicles and care should therefore be taken not to over diagnose seminal vesicle involvement if tumour is adjacent to fragments of ejaculatory duct.

**Prostate TUR Chippings**

Prostatic carcinomas are often an incidental finding in prostate chippings and are usually transition zone tumours, unless the tumour is an extensive peripheral zone malignancy.

Prostatic carcinoma is difficult to reliably identify macroscopically, therefore random sampling of chippings needs to be sufficient to detect low volume pT1a tumours and to determine when carcinomas are stage pT1b. Chippings should be weighed and then sampled. Eight blocks will identify most pT1b cancers. Additional sampling depends on the amount of remaining tissue, whether or not there is a suspicion of carcinoma or whether radical treatment would be contemplated, but with a common sense approach if the amount of tissue is extensive. Guidance is given in the RCPath Minimum Dataset.

If histology reveals a carcinoma, the diagnostic features described above and the percentage of chippings involved by tumour should be stated (<5% = pT1a, >5% = pT1b). High grade low volume tumours are also regarded as pT1b for treatment.

**Radical Prostatectomy**

Radical prostatectomies are preferably processed in their entirety (excluding the tips of the seminal vesicles) as macroscopic identification of prostate cancer is difficult.

The prostate should be weighed and 'inked' prior to slicing to enable easy orientation of the subsequent H&E stained sections. Different coloured inks may be used, such as a two-colour system to indicate the left and right halves, or additional colours as preferred. Slicing prior to adequate fixation risks distortion and warping of slices, particularly if there is nodular hyperplasia, unless the slices are pressed flat to fix.

The apex (inferior aspect) of the gland is preferably amputated and ‘coned’ to enable this margin to be clearly assessed. The basal (superior aspect) is less often found to contain tumour and may be ‘shaved’ or ‘coned’ depending on the size of the gland. The remainder of the gland should be sliced horizontally into 3-5mm slices and processed either in Megablock sections or in small blocks (with each slice divided into quadrants). Megablocks enable easy orientation of the tissue slices and demonstration of the tumour site, but are slower to process and more difficult to handle if immunostains are required. A photograph of the sliced gland may be helpful in later demonstration of tumour site and relationship to specimen margins.
The microscopy report on the prostatic carcinoma in radical prostatectomy specimens should contain information specified in the RCPath guidelines, as previously described above. In addition, the following should be noted, with assessment of TNM stage:

- **Tumour volume**
  Formal tumour volume measurements are not normally undertaken in routine practice, but some indication of the extent of tumour involvement, such as an estimated percentage and/or measurement of size of dominant nodules, and whether the tumour is multifocal or unifocal should be included.

- **Extra-prostatic tumour spread**
  The anterior surface, apical and basal margins are areas where the boundaries of the gland are most difficult to define and extra-prostatic spread is therefore difficult to assess. The dorso-lateral aspects are the most common sites for extra-prostatic spread. If present, an indication of whether such spread is focal or extensive should be given.
  Evidence of microscopic invasion of bladder muscle at the base, or invasion of the muscular wall of the seminal vesicles, if present, should be stated.

- **Surgical margins**
  A margin is not considered to be positive unless the tumour directly contacts the ink. If the tumour contacts the margin, it should be clear from the report whether this is an intra-prostatic margin (where there is a surgical incision into the gland) or whether the tumour is at the limit of the gland ‘capsule’ and no extra-prostatic tissue is present for assessment at this site (variably called pT2+ or pTX if no extra-prostatic spread is seen elsewhere ) or whether it is a positive extra-prostatic margin.

- **Lymphovascular invasion**
  If lymphovascular invasion identified in the prostatectomy specimen, this should be noted in the report. All the regional nodes in associated lymphadenectomy specimens should be processed and examined microscopically to determine whether there is metastatic tumour spread.

**Cases referred to cancer centre for review presentation at MDT meeting**

The following should be dispatched to the Urology MDT Co-ordinator:

- Copy of original histology report and any relevant previous histology reports
- All of the original slides and any previous relevant previous histology slides

Blocks are not initially required, but may be requested.

The slides and blocks will be returned as soon as possible after review and the MDT meeting, along with a copy of the review histology report.
Appendix 2 – Staging of Prostate Cancer

TNM Classification of Prostate Cancer (TNM 2002 edition)

**TO**  
No evidence of primary tumour

**TX**  
Primary tumour cannot be assessed

**T1**  
Clinically unapparent tumour, impalpable and not visible by imaging  
- **T1a** Tumour an incidental finding in \(< 5\%\) of resected tissue  
- **T1b** Tumour an incidental finding in \(> 5\%\) of resected tissue  
- **T1c** Tumour identified by needle biopsy (e.g. because of raised PSA)

**T2**  
Tumour confined within prostate  
- **T2a** Tumour involves \(<\) half one lobe  
- **T2b** Tumour involves \(>\) half a lobe but not both lobes  
- **T2c** Tumour involves both lobes

**T3**  
Tumour extends through the prostate capsule  
- **T3a** Unilateral or bilateral extracapsular extension  
- **T3b** Tumour invades seminal vesicle(s)

**T4**  
Tumour is fixed or invades adjacent structures – i.e. bladder neck, external sphincter or rectum, levator muscles or fixed to pelvic side wall

**Regional Lymph Nodes**  
- **NX** Nodes cannot be assessed  
- **N0** No regional lymph node metastases  
- **N1** Regional lymph node metastasis

**Distant Metastases**  
- **MX** Distant metastasis cannot be assessed  
- **MO** No distant metastasis  
- **M1** Metastasis

**Whitmore-Jewett Staging System**

- **A1** Microscopic focus of well-differentiated adenocarcinoma in up to three foci of transurethral specimens or enucleation; clinically not apparent on rectal exam.  
- **A2** Tumour not well differentiated or present in more than three areas  
- **B1** Asymptomatic palpable nodule \(<1.5\text{cm}\); normal surrounding prostate; no capsular extension; normal acid phosphatase  
- **B2** Diffuse involvement of gland; no capsular extension; normal acid phosphatase  
- **C** Extension local tumour with penetration through the capsule; contiguous spread may involve seminal vesicles, bladder neck, lateral side wall of pelvis; acid phosphatase may be elevated; normal bone scan  
- **D1** Metastases to pelvic lymph nodes below aortic bifurcation; PSA may be elevated  
- **D2** Bone or lymph node metastases above aortic bifurcation or other soft tissue.
Appendix 3 - Advice for the use of hormone therapy

**Orchidectomy** As there is no urgency for surgery, start on antiandrogen and then LHRH analogue (see guidelines above). Refer to Consultant Urology Surgeon - after surgery stop hormones.

LHRH analogue *e.g.* goserelin. An Antiandrogen should be given for a minimum of three days before the first dose of LHRH analogue, and for three weeks after the first injection. An information sheet should be given to the patient describing the likely and possible side effects of hormones – the patient should clearly understand that it is his responsibility to make an appointment with the GP for the next depot injection (the this fact should also be written on the advise sheet). Write to GP with a clear indication of the date of the next injection and the treatment duration.

**Bicalutamide monotherapy** 150 mg po o.d. Reported to be as effective in monotherapy and better tolerated than LHRH analogue - little hot flushes, low incidence of impotence, depression and bowel disorders. If long-term treatment is planned prophylactic breast bud irradiation should be considered to prevent gynaecomastia. This dose is expensive and doesn’t reduce the PSA as low as LHRH analogue.

**Cyproterone acetate** CPA 100 mg po tds. Not as effective as LHRH analogue and has a 10% of significant liver damage. Should be reserved for men who cannot tolerate bicalutamide or LHRH analogue as does not cause hot flushes.

**Oestrogens** Diethylstilboestrol 1-3 mg od. Still remains a very effective treatment particularly when the tumour has become resistant to the other hormones and should only be considered third line. Gynaecomastia should be prevented by radiotherapy to both breast buds. The risk of thromboembolism reduced by giving aspirin 75mg. In patients with a history of thromboembolic disease consider warfarin 1 mg od. Warfarin requires an INR test at 2 - 4 weeks - If this value is below 2 then it does not require measuring again. A recent study suggests that the use of Aspirin is preferred to Warfarin (Ref: Clinical Oncology 2004:(16);505-516).
Appendix 4 – Further radiotherapy details

Radiotherapy details  CT planned. Three fields; two lateral beams and an anterior beam using 15 mv if possible. Conformal planning is now routinely available. Planning target volume should include Prostate plus 1cm and base of seminal vesicles. Seminal vesicles should be included if evidence of involvement on MRI or CT. If the seminal vesicles look normal on scanning the decision to treat them can be helped by the following formula (Diaz et al 1994):-

<table>
<thead>
<tr>
<th>LOW RISK</th>
<th>MODERATE RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>All T1a-b</td>
<td>All T2c, T3a-c</td>
</tr>
<tr>
<td>T1c -T2a-b with PSA + [(Gleason score -6) x 10] = \leq 15</td>
<td>T1c -T2a-b with PSA + [(Gleason score -6) x 10] = \geq 15</td>
</tr>
</tbody>
</table>

In a young otherwise fit man with adjacent positive nodes, consider a two phase volume treating the pelvic nodes first then just the prostate and adjacent nodes.

Radiotherapy dose  
- Radical 74Gy in 37# over 7.5 weeks  
- Radical alternative 50 – 55 Gy in 20# over 4 weeks  
- Radical hypofractionated dose 30Gy 6# 2 weeks  
- Palliative radiotherapy or 20 - 30 Gy in 5-10#
Appendix 5 - Clinical Trials Supported by the Network

Prostate trial portfolio for site specific group:

Summary:-

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Status</th>
<th>NCRN Trial</th>
<th>WACRN Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 30985</td>
<td>P</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>EORTC 30991</td>
<td>O</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>PR07</td>
<td>O</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>ProtecT</td>
<td>O</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>CHHIP</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Details:-

Trial ID          | Trial Objective                                                                                                                                                                |
------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
EORTC 30985       | A Phase III trial of Intermittent androgen deprivation in patients with stage D2 prostate cancer.                                                                              |
EORTC 30991       | A randomized Phase III step-up study on initial antiandrogen monotherapy in comparison with watchful waiting in asymptomatic T1-3 any G (any Gleason) N0 or NxM0 prostate cancer patients without local treatment with curative intent. |
PR07              | A randomised trial of hormone therapy plus radical radiotherapy versus hormone therapy alone in non-metastatic prostate cancer.                                                  |
ProtecT           | The ProtecT Trial - Evaluating the effectiveness of treatment for clinically localised prostate cancer.                                                                     |
CV247             | A randomized double blind study of CV247 versus salicylic acid both with dietary modification. Open to patient considered for watchful monitoring either pre or after local therapies. – contact Dr Robert Thomas Bedford or www.cancernet.co.uk (trials)
CHHIP Conventional or Hypofractionated High dose Intensity Modulated Radiotherapy for Prostate Cancer

Part 2 of this trial is currently open to recruitment and is primarily aimed at assessing the acute and late side-effects of high dose hypofractionated IMRT compared to conventionally fractionated high dose radiotherapy treatment. Aspects of recurrence free and overall survival and quality of life issues form the basis of the third part of this trial due to open on completion of part 2 around April 2006.
Appendix 6 - Patient Information Sheet

Spinal Cord Compression

Your doctor has explained that your cancer has unfortunately spread to some of the bones. In some patients the disease can spread further to involve the bones in the spine. If this occurs it can interfere with messages passed by the spinal cord. This can produce numbness and paralysis. Although this is rare, it can be treated effectively. Results are best if patients are seen early.

Warning Signs

The earliest warning sign is severe persistent pain in the spine which passes around the chest or abdomen or shoots down the arm or leg. The pain is severe and persistent and usually precedes other symptoms by some weeks.

Other symptoms include:

- Pain starting in the back and passing around the chest or abdomen.
- Back pain which is not relieved by rest or which wakes you from sleep.
- Numbness and tingling of the legs or body.
- Weakness of the legs.
- Difficulty in standing or walking.

What to do

If these symptoms develop you should arrange to be seen urgently by your GP who will then arrange urgent assessment at hospital if appropriate.

Not all patients with pain have spinal cord compression but numbness and weakness of the legs are highly suspicious. If in doubt you may wish to show this leaflet to your doctor.
Appendix 7 – IV Bisphosphonate Guidelines

GUIDELINES FOR THE USE OF INTRAVENOUS BISPHOSPHONATE THERAPY IN PATIENTS WITH PROSTATE CANCER AND BONY METASTATIC DISEASE.

All patients with hormone refractory symptomatic bony metastatic disease should be considered for IV bisphosphonate therapy using Zoledronate 4mg (modified according to renal function) 3-4 weekly. Treatment should include calcium and vitamin D supplementation using Adcal D3 1 tablet b.d. or an appropriate alternative. In the absence of clear data from the literature it seems reasonable to offer the treatment for a 6 month period and then review further therapy in the light of perceived future benefit.

For patients with a very short life-expectancy the benefit of this treatment uncertain, and the treatment should be offered on an individual patient basis.

Patients with asymptomatic bony metastatic disease can also be considered for treatment on an individual basis, particularly if they have predominantly lytic disease.
Appendix 8 – Osteoporosis Guidelines

GUIDELINES FOR THE PREVENTION AND MANAGEMENT OF OSTEOPOROSIS IN PATIENTS WITH PROSTATE CANCER EXPECTED TO RECEIVE PROLONDED ANDROGEN DEPRIVATION.

Dr Helen Patterson, Professor Juliet Compston.

This recommendation relates to patients on:

1. Indefinite LHRH analogue therapy or
2. Three years of adjuvant androgen deprivation following radical radiotherapy.

Bone densitometry (hip and lumbar spine) should be requested at the time the decision to initiate LHRH analogue therapy is made.

If the T score is -2.5 or worse at initiation of LHRH analogues then patients should commence treatment with oral bisphosphonates eg. Alendronate 70mg po once weekly or Risedronate 35mg po once weekly with calcium and vitamin D supplementation eg Adcal-D3 one tablet b.d., Calcichew D3 forte one b.d. or Calcit D3 one b.d.

If the T score is -2 or worse perform lateral thoracic and lateral lumbar spine films to exclude a pre-existing crush vertebral fracture as 2/3 do not come to medical attention, and patients who experience a vertebral fracture have a 20% incidence of a further fracture over the ensuing 12 months. If a fracture is identified, commence treatment as above with oral bisphosphonates, calcium and vitamin D.

If the T score is -2 or better patients should be considered for calcium and vitamin D supplementation and repeat densitometry at a later date to monitor progress (the densitometry report will usually advise as to scan interval).

In addition, any patient considered to be at increased risk (see below) of osteoporosis, prior to the commencement of LHRH analogue therapy, should also be considered for bisphosphonate therapy.

Past history of fragility fracture.
Concurrent corticosteroid therapy.
Low body mass index <19kg/m².
Heavy smoking.
High alcohol intake.

There are national guidelines which state that anyone over the age of 65 years started on any dose of oral corticosteroid expected to be continued for more than 3 months should be offered oral prophylaxis against osteoporosis with a bisphosphonate, either Alendronate 70mg once weekly or Risedronate 35mg once weekly together with calcium and vitamin D supplementation as above.

Patients expected to undergo short-term LHRH analogue therapy (neo-adjuvant and concurrent with radical radiotherapy alone) do not need to undergo routine bone densitometry.
For patients who are on treatment for known osteoporosis, LHRH analogue therapy should still be considered the treatment of choice to accompany their radical radiotherapy treatment unless other issues indicate the use of bicalutamide.
Appendix 9 – Radical Radiotherapy Post-Radical Prostatectomy

Immediate radical radiotherapy to the prostate bed following radical prostatectomy in patients with pT3 disease significantly improves 5 year biochemical progression-free survival (74.0% vs 52.6%) when compared with watchful waiting (p<0.0001). The cumulative risk of locoregional failure at 5 years was also improved (5.4% vs 15.4% p<0.0001). There was a statistically significant benefit for immediate irradiation in all risk groups including those with negative margins, those with seminal vesicle involvement and those with a recordable PSA post-prostatectomy (Bolla et al., 2005). Weigel et al. also reported an absolute 21% improvement in bNED at 4 years (81% vs 60%) in 385 patients similarly randomised to adjuvant radiotherapy or a wait and see policy. In both studies the radiotherapy was very well tolerated.

In a multivariate analysis of 501 patients undergoing salvage radiotherapy for a rising PSA post-radical prostatectomy Stephenson et al. (2004) identified 5 independent adverse prognostic variables for a durable response to salvage radiotherapy:

- Gleason 8-10
- Pre-radiotherapy PSA>2.0ng/ml
- Negative surgical margins
- PSADT<=10 months
- Positive seminal vesicles

With the exception of pre-radiotherapy PSA level >2ng/ml (where numbers were very small), the presence of only one of these adverse risk factors was not associated with a high risk of an adverse outcome to salvage radiotherapy, and radiotherapy should be considered in these patients. However, only around 20% patients with 2 or more of these features achieved a durable response to salvage radiotherapy and this figure should be born in mind when counselling such patients as to their likely outcome with radiotherapy treatment.

It seems reasonable therefore to offer patients with pT3 pN0 disease at prostatectomy early adjuvant radiotherapy to the prostate bed, after discussion at the SMDT. They should be counselled regarding the risks associated with salvage radiotherapy, particularly the expected increased risk to their urinary continence and remaining potency. The risk of grade 3 urinary frequency/dysuria and rectal toxicities do appear reassuringly low (no higher than with prostate radiotherapy alone).

The Bolla trial does not however directly compare adjuvant post-operative radiotherapy with early salvage radiotherapy and the latter may offer similar advantages. For patients with continence problems or for whom it is important to maintain potency it seems reasonable to offer a policy of surveillance with 2-3 monthly PSA measurements and prompt oncology referral for a confirmed rising PSA.

Alternatively some of these patients will be eligible for randomisation in the ATLAS trial which is comparing immediate versus deferred adjuvant LHRH analogue therapy (18 months) +/- 6 cycles of docetaxel in patients at high risk of recurrence post radical prostatectomy. Patients who may be particularly suitable for ATLAS rather than adjuvant RT are those with LN or seminal vesicle involvement as well as capsular invasion and Gleason 8-10 disease.
Radiotherapy Planning Technique

When available use pre-operative pelvic imaging/surgical clips in the prostate bed as well as histopathology report of positive margins to define the CTV.

The clinical target volume (CTV) should include the prostate bed, the anterior rectum adjacent to the prostate bed and the bladder base, with a 1cm margin for planning target volume (PTV) to CTV. Consider sparing the urethral bulb if the maintenance of potency is an important issue and the apical margin is clear.

Single phase:

Dose 64Gy/32#/6.5 weeks or 52.5 or 55Gy/20#/4 weeks.

References


*Helen Patterson 30.09.2005*