Greater Manchester and Cheshire NHS

Cancer Network

PROSTATE CANCER GUIDELINES

Agreed by Urology CSG: July 2010

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PROSTATE CANCER

1 INITIAL REFERRAL FROM GP

GPs will follow the existing guidelines for the referral of suspected prostate cancer produced by NICE in 2005. (NICE Guideline – "Referral guidelines for suspected cancer" (2005))

Prostate cancer

- Patients presenting with symptoms suggesting prostate cancer should have a digital rectal examination (DRE) and prostate-specific antigen (PSA) test after counselling.
- Prostate cancer is also a possibility in male patients with any of the following unexplained symptoms:

  • erectile dysfunction

  • haematuria

  • lower back pain

  • bone pain

  • weight loss (especially in the elderly).

  These patients should also be offered a DRE and a PSA test where appropriate.
- Urinary infection should be excluded before PSA testing, especially in men presenting with lower tract symptoms. The PSA test should be postponed for at least 1 month after treatment of a proven urinary infection.
- If a hard, irregular prostate typical of a prostate carcinoma is felt on rectal examination, then the patient should be referred urgently. The PSA should be measured and the result should accompany the referral. Patients ***do not*** need urgent referral if the prostate is simply enlarged and the PSA is in the age-specific reference range.
- In a male patient with or without lower urinary tract symptoms and in whom the prostate is normal on DRE but the age-specific PSA is raised or rising, an urgent referral should be made. In those patients whose clinical state is compromised by other co-morbidities, a discussion with the patient or carers and/or a specialist in urological cancer may be more appropriate prior to deciding whether or not the referral is urgent.

- Symptomatic patients with high PSA levels should be referred urgently.
- If there is doubt about whether to refer an asymptomatic male with a borderline level of PSA, the PSA test should be repeated after an interval of 1 to 3 months. If the second test indicates that the PSA level is rising, the patient should be referred urgently. If the PSA is stable but raised a routine appointment should be made.

2 INITIAL ASSESSMENT AND TRUS BIOPSY

Suspected prostate cancer patients will be seen in Urological departments hosting clinics assessing prostate cancer. These clinics must have the facilities for counselling, digital rectal examination (DRE), PSA testing and TRUS/needle biopsy undertaken by suitably trained healthcare professionals. They must also have the facility for specialist histological evaluation and relevant imaging.

All trans-rectal biopsies should be ultrasound guided, taken after infiltration with local anaesthetic and be carried out under antibiotic cover according to an agreed unit policy. The presence or absence of visible abnormalities should be noted. The prostate gland volume or its 3 dimensional measurements should be recorded in the case records.

A minimum of 12 systematic biopsy cores should be taken, directed towards the peripheral zone. Focal abnormalities should be biopsied. More than 12 biopsy cores may be required in some circumstances.

A repeat biopsy should be considered:

- A rising and/or persistently raised PSA
- A suspicious DRE
- Atypical small acinar proliferation (ASAP)

If the PSA remains high in the presence of a normal biopsy a second biopsy should be undertaken within 3 to 6 months.

3 DIAGNOSIS, STAGING AND RISK ASSESSMENT

An accurate clinical stage must be assigned to every patient.

Biopsies should be graded histopathologically using the Gleason grading system and be reviewed in an MDT or SMDT.

The number of positive cores, the percentage of involvement of the cores and their lateralisation should be recorded.

Standard published nomograms may be used to aid patients' decision making.

Patients should be allocated a risk category using the following criteria:

Low risk

- cT1-T2a and Gleason <7 and PSA <10ng/ml
- % of involved cores <50%

Intermediate risk

- cT2b-T2c and/or Gleason 7 and/or PSA 10-20ng/ml
- Low risk features with >50% involved cores

High risk

- cT3-T4
- Gleason 8-10
- PSA>20ng/ml or

Patients should have an attempt at assessing life-expectancy and/or degree of co-morbidity present, ideally with a validated tool (e.g. Charlson index or Adult Co-morbidity Evaluation-27 (ACE-27)).

Patients with Low risk prostate cancer require no staging investigations.

Patients with intermediate risk disease with PSA >10 should be considered for, and those with high risk prostate cancers should have staging investigations for nodal status and the presence or absence of distant metastatic disease. At present, CT or MR scanning are equally acceptable for nodal imaging, and bone scanning and / or axial MR for bony metastases.

Local staging of the prostate with MR scanning may be helpful in specific clinical scenarios, preferably under direction of the SMDT.

There is no current indication for PET scanning in prostate cancer outside the aegis of a clinical trial.

Patients with clinically localised prostate cancer must be discussed in a Specialist MDT and a management plan formulated by the SMDT.

4. TREATMENT

Treatment options for Clinically Localised Prostate Cancer

Risk Group	Available options*
Low Risk	Active surveillance Watchful Waiting LDR Brachytherapy Radical Prostatectomy Radical External Beam Radiotherapy
Intermediate Risk	Active surveillance (selected cases) Watchful Waiting (advanced age/co-morbidity) LDR Brachytherapy Radical Prostatectomy Radical External Beam Radiotherapy HDR brachytherapy + EBXRT
High Risk	Radical Radiotherapy External beam radiotherapy + Adjuvant Hormones HDR brachytherapy + EBXRT with Adjuvant hormone therapy Radical Prostatectomy Hormone therapy alone (where radiotherapy or surgery is contra-indicated Watchful waiting (advanced age/co-morbidity

Active Surveillance

Four monthly monitoring of PSA and DRE for 2 years and 6 monthly thereafter. The timing and role of repeat TRUS/Bx is unclear but this may considered on an annual basis. Triggers for active treatment may include patient choice, rising PSA, progression on clinical stage or upgrading on biopsy.

Watchful Waiting

Suitable for patients, usually of advanced age or with serious medical co-morbidity who are not considered appropriate for radical local treatment. Patients should be monitoring using PSA and clinical examination. Hormone manipulation may be commenced at a predetermined level of PSA or following signs of clinical progression. Other symptoms such as lower urinary tract symptoms should be treated as appropriate by standard urological means.

Radical Prostatectomy

All patients should have an assessment of their pre-operative urinary and sexual function. The SMDT should take these into account when recommending surgery with particular reference to the intent/suitability for nerve sparing. Patients should be given written information and be suitably counselled about the risks involved with surgery, particularly in relation to urinary and sexual function. This counselling should include information about the need for post operative radiotherapy in the event of high risk features. This may be in the context of the RADICALS trial. All options of surgery should be discussed including traditional laparoscopic and robot assisted laparoscopic prostatectomy, and referral onwards should be made as appropriate and in accordance with the patients wishes and opinion of the referring urologist.

Lymphadenectomy should be performed in high risk cancers and it may be considered in intermediate risk cancers.

Radical prostatectomy specimen histopathology reports should comment on the following:

- Gleason grade of tumour/s
- Side/s involved
- Pathological stage
- Volume / size of tumour nodule/s
- Margin positivity
    - Number
    - Site
    - Consider commenting on length of positive margin (e.g. <1mm)
    - Grade of tumour at margin
- Presence/absence of perineural infiltration and lymphovascular invasion

External Beam Radiotherapy (EBXRT)

Patients should be treated with conformal radiotherapy with use of intensity modulated treatment where appropriate.

Neoadjuvant hormone treatment

- The current standard of care for locally advanced (T3NoMo) prostate cancer is combination treatment with radiotherapy and long term hormones; although there are some circumstances where radical prostatectomy ± local radiotherapy may be considered. Normally, patients with T3 disease, Gleason Score ≥7 or PSA ≥10 should be treated with 3 months neoadjuvant therapy using LHRH analogues (with initial 2-3 weeks anti-androgen cover with cyproterone acetate 100mg TDS or bicalutamide 50mg OD) prior to EBXRT. This should then be followed with adjuvant androgen deprivation treatment for a minimum of 2 years.
- NeoAdjuvant hormones may also be used in selected patients considered otherwise suitable for brachytherapy who present with prostate volumes 50-70mls.

Informed consent for planning and treatment

- Acute and late side effects are covered in the 'radiotherapy to the prostate' booklet: www.christie.nhs.uk/patients/booklets/text/radiotherapy/prostate.aspx

The patient should be given written information regarding radiotherapy treatment and early and late side effects, including the risk of second malignancy, prior to decisions being taken regarding treatment.

Radiotherapy planning

Radical radiotherapy

<u>Conformal radiotherapy</u>

- Patients are CT scanned in the supine position, with an empty bladder.
- Single phase technique:

  The CTV is the whole prostate, plus base of the seminal vesicles. The whole seminal vesicles are included if the patient is known to have involvement/ high risk of seminal vesicle involvement depending on prognostic factors.

  The PTV is the CTV plus a margin of 1cm in all directions except posteriorly where the margin is 0.7cm.

OAR include the rectum, bladder, small bowel and femoral heads.

- 2 phase technique:

  Phase 1 PTV is as for 3D conformal technique

  Phase 2 PTV is prostate alone

  OAR as above.

- IMRT plans:

  Prostate and seminal vesicles are outlined separately and OARs rectum, the bladder and femoral heads are also outlined.

Verification

- Patients have MVIs (XVIs if on Suite 10) days 1, 2 & 3 and weekly thereafter if set up is within 3mm tolerance.
- If the average of set up error is not within tolerance, a move is calculated by radiographers and patient is then re-imaged on the subsequent 3 days.

Low Dose Rate Brachytherapy (LDR)

Informed consent for planning and treatment

Patients attend for a volume study prior to brachytherapy. Patients are suitable if the prostate volume is <60 cc and the pubic arch not occlusive. If there is pubic arch interference, the patient is advised to have EBXRT.

Acute and long term side effects can be found in the prostate brachytherapy booklet:
www.christie.nhs.uk/patients/booklets/text/prostate_brachytherapy/default.aspx

The patient should be given written information regarding radiotherapy treatment and early and late side effects, including the risk of second malignancy, prior to decisions being taken regarding treatment.

Brachytherapy planning

- Patients attend for volume study 1-2 weeks prior to brachytherapy. Prostate volume is assessed and images taken to plan co-ordinates for seed insertion.

- Organs at risk are the urethra and rectum.
- Patients are admitted as a day case for the procedure and are given a phosphate enema.
- I^{125} seeds are inserted to the whole prostate under USS guidance in radiotherapy theatre and catheter inserted.
- Once seeds are inserted a plain pelvic XR is taken for verification.
- Catheter is removed immediately post treatment and patients may go home once voiding urine satisfactorily.
- Ibuprofen 400mg tds PRN and Ciprofloxacin 500mg bd is given for one week, and Tamsulosin 400mcg to take until their next urology review.

Doses

- Dose 145Gy prescribed to the 100% isodose with aims to encompass the prostate with a small margin of between 3-5 mm. (MINIMAL PERIPHERAL DOSE).
- ≥99.5% of volume to receive 145Gy, <55% of prostate volume to receive 150% (217.5Gy), <20% of prostate to receive 200% (290Gy).
- Vol. of Urethra to receive ≥150% (217.5Gy) = 0.03 cm^3, Vol. of Rectum to receive ≥100% (145Gy) = 0.4 cm^3 (and ≤2cm^3 to receive ≥100Gy).

High Dose Rate Brachytherapy (HDR)

- This is an alternative approach to IMRT for dose escalation and is used in combination with neo-adjuvant hormone treatment and EBXRT.
- Patients are warned to expect the same side effects as for LDR brachytherapy and radical radiotherapy.
- Patients are admitted the morning of treatment and given a phosphate enema.
- Applicators are inserted into the prostate through a grid under TRUSS guidance.
- All planning is done using ultrasound with the applicators in place and dose distribution (Iridium-192 dwell times) is then calculated.

- A dose of 12.5Gy prescribed as the minimal peripheral dose to the 100% isodose as a single fraction is delivered whilst patient is still under general anaesthetic.
- Patient may be discharged the same day once voiding urine successfully.
- HDR is followed by 37.5Gy in 15# EBXRT 2 weeks later.
- Acute and long term side effects are detailed in the HDR booklet: www.christie.nhs.uk/patients/booklets/text/radiotherapy/hdr_brachytherapy.aspx

Follow up

Patients are seen weekly through their radiotherapy treatment.

For bowel frequency, Fybogel +/- Loperamide is prescribed.

For obstructive urinary symptoms, Tamsulosin is prescribed

Six week telephone follow up is arranged following completion of XRT. Patients who have brachytherapy are seen in the clinic six weeks post treatment.

Patient follow-up is then shared between the referring urologist and oncologist and the patient is seen for review every 6 months.

At each follow up visit the PSA is documented and information regarding bladder/ bowel habit and sexual function is made.

Patients are discharged after 5 years of uneventful follow up.

Hormone Therapy

High risk patients not considered suitable for treatment with curative intent, usually due to the presence of significant co-morbidity, can be offered hormone manipulation alone.

However, in light of recent level 1 evidence of benefit, all patients should be considered for external beam radiotherapy to the prostate in addition to receiving ADT.

In patients receiving ADT only, Non-steroidal anti-androgen monotherapy may be considered and intermittent therapy may be used according to protocols defined by the SEUG trial (Da Silva et al Eur Urol 2009).

Other Treatment Options

High Intensity Focused Ultrasound (HIFU), cryotherapy or focal therapy are unproven modalities and are regarded as experimental procedures. They should only be considered within the context of a properly constructed clinical trial or a strictly defined and agreed protocol with full audit and monitoring procedures.

TREATMENT FAILURE AFTER CURATIVE THERAPY

Definition

After Radical Prostatectomy

- Residual or recurrent PSA elevation of 0.2ng/L three months or more following surgery

After Radical Radiotherapy

- PSA value of 2ng/ml above the nadir can be considered as failure. The phenomenon of PSA Bounce must be considered when making this assessment.

Patients diagnosed with PSA failure need to be assessed for local or systemic relapse.

Imaging studies and biopsy of urethral-vesical anastomosis site is usually unhelpful following radical prostatectomy. Useful parameters include:

- Timing of PSA failure after surgery
- PSA DT
- PSA velocity

Local failure is implied post radiotherapy in the presence of negative staging investigations. Prostatic biopsies should be considered and are mandatory if local salvage treatment is contemplated.

Treatment

Local failure following RP:

- Should be considered for salvage radiotherapy to prostatic bed
- Entry into the NCRI RADICALS trial should be offered to all patients

Local failure following radiotherapy:

- Salvage radical prostatectomy may be considered in carefully selected patients
- Other local treatment options such as cryotherapy or HIFU should only be delivered in carefully controlled and audited protocols, or in a clinical trial setting.

Systemic failure

- Patients with suspected or proven systemic failure should be counselled about hormone manipulation.
- Entry into clinical trials should be considered and encouraged.

METASTATIC DISEASE

Patients should be treated with hormone manipulation. This will comprise administration of GnRH analogues or surgery with orchidectomy. Anti-androgens or GnRH antagonists may be considered in some circumstances. GnRH analogue therapy should be accompanied by anti-androgens to cover tumour flare at the start of treatment. In patients at high risk of osteoporosis bone preservation with bisphosphonates or RANK ligand inhibitors should be considered.

All patients notwithstanding their stage of disease should be considered for entry into research trials where appropriate.

Management of Hormone Refractory Disease

Second line therapy with anti-androgens should be considered in the event of treatment failure following primary ADT. Anti-androgens such as Bicalutamide are usually considered for first line. Low dose oestrogens with supplementary aspirin may also be used after appropriate counselling about increased cardiovascular risk. Chemotherapy using currently proven drugs should be considered for appropriate patients and where possible this should be under the aegis of a clinical trial.

Bisphosphonates or RANK Ligand inhibitors should be considered where there is a significant risk of skeletal problems.

Patients with painful bone metastases should be considered for treatment with radiotherapy or radionuclides where appropriate. Bisphosphonates and/or steroids may also be used in this situation. Patients with, or at high risk of, pathological long bone fracture should be referred urgently to a specialist centre for treatment.

Patients with signs of spinal cord compression must be started on steroids and assessed urgently before referral, within 24 hours, for consideration of treatment.

Patients with obstructive renal failure should be counselled about nephrostomy and/or ureteric stenting. Where this is appropriate, this should be undertaken by experienced radiologist. Chronic/progressive anaemia should be treated with blood transfusion. Erythropoietin may be considered in certain circumstances.

Patients should receive palliative support working within the framework of the MDT.

Patients should be considered for entry in to available clinical trials.

5 FOLLOW-UP

Where there are agreed protocols between secondary care and GPs practices, shared care may be undertaken

Patients undergoing treatment for prostate cancer should be followed up either in the local Urology units, in the cancer centre or in a combination of both.

6 PATIENT INFORMATION AND SUPPORT

A key worker should be identified to facilitate patient access for treatment counseling and support.

7. PATHOLOGY REPORTING

All cases shall be reported in accordance with the Royal College of Pathologists standards and datasets. This document can be found at www.rcpath.org.uk and in the network guideline document “Pathology Guidelines for Urological Cancers”.