Improving the diagnosis and treatment of high-risk localised or locally advanced prostate cancer

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Radiologists, oncologists, urologists and clinical nurse specialists met to evaluate how patients with high-risk localised or locally advanced prostate cancer might be better diagnosed and managed. In this first article, the authors look at ways in which the diagnosis of the disease could be improved and discuss how to optimise hormonal and radiotherapy. The second article in the series will evaluate surgical therapy.

One of the most challenging areas of prostate cancer is the management of patients with high-risk localised or locally advanced disease (stage T3-T4, Nx-N0, M0; Figure 1). The problem with a single definition, such as that of D’Amico,1 is that it does not take into consideration the heterogeneity of this group of patients whose post-surgical pathological T stage can be higher or lower.2,3 In addition, it does not consider indicators of disease load, such as biopsy core involvement or occult lymph node positivity, the latter being as high as 40% in this group.4 Also, the various guidelines relating to treatment of high-risk disease do not provide a cohesive therapeutic strategy. A number of studies have reported the benefits of using a genomic classifier, a 22-gene expression panel test, to predict metastatic disease following surgery, but further validation is required.5

Radiological diagnosis of high-risk prostate cancer

The radiological objective in high-risk localised prostate cancer patients is to detect those men with extraprostatic disease, but without distant metastases, who should be offered additional multimodality therapy. The current NICE recommendation for imaging in the UK is...
for men with biopsy-confirmed prostate cancer who may be suitable for radical curative therapy or active surveillance to be considered for pelvic MRI, or CT scan where MRI is contraindicated.6

There is growing interest in the use of multiparametric MRI prior to biopsy. This has two purposes: to be able to direct the biopsy to maximise the detection of higher risk disease,7 and to provide accurate local staging information, without the post-biopsy artefact, which can lead to under- or overstaging. While a number of centres across the UK and beyond are adopting this strategy, it is not yet standard practice. In order to determine accurately whether standard biopsy or MRI-targeted biopsy is more accurate in the detection of higher risk disease, a set of internationally agreed reporting standards for MRI-targeted biopsy studies has been developed (the START criteria).8

Radiological staging of the prostate
MRI for prostate cancer was first developed as a staging tool, using anatomical sequences (T1- and T2-weighted imaging) to assess for local invasion and nodal disease. The addition of functional parameters has allowed the detection of areas of higher risk prostate cancer within the gland, which can be used to direct both biopsy and treatment. All agreed that pictorial reporting of the MRI to show the location of disease was a critical component of the MRI report.

The European Society of Urogenital Radiology guidelines give specific criteria for their structured reporting scale, which they call the Prostate Imaging and Reporting Archiving Data System (PI-RADS). This includes specific criteria for the likelihood of extracapsular disease, which include capsular abutment, irregularity and loss of capsule, as well as radiological criteria for the prediction of seminal vesicle, distal sphincter and bladder neck involvement.9

**Radiological assessment for nodal disease**
Size criteria are applied to define nodal spread; a node is considered pathologic when the minimal axial diameter is ≥10mm or when the maximal axial diameter is 8–10mm and the ratio of the short to long axis is >0.8 (a round node).10 These measurements can be made on CT or anatomical MRI images (T2-weighted). The problems with using size criteria are that they fail to detect metastases in normal sized nodes and have difficulty in distinguishing between large hyperplastic (benign) nodes and malignant nodes. The gold standard for diagnosis of lymph node involvement remains extended lymph node dissection; however, due to the morbidity associated with this procedure it is recommended only for those more likely to have lymph node involvement. In comparison to this gold standard, CT and conventional MRI have an average specificity of around 80%, and sensitivity of around 40%.11 The latest NICE guidelines recommend use of pelvic CT for staging only when MRI is contraindicated.9

**Radiological assessment of distant metastases**
The standard approach to the detection of bone metastases in men with high-risk prostate cancer is ⁹⁹Technetium (⁹⁹Tc) bone scintigraphy. While it has an established high sensitivity for osteoblastic metastases, early work shows that whole-body diffusion-weighted (WB-DWI) MRI is able to detect more malignant lesions per patient and fewer benign lesions compared with planar bone scans.12 A single WB-DWI MRI scan to replace pelvic MRI and ⁹⁹Tc bone scan has been proposed.13 This would streamline the patient pathway, using MR scanning time at the expense of nuclear medicine time. The standard recommendations in the UK, Europe and the USA are still for ⁹⁹Tc bone scan for the evaluation of distant metastases, with MRI or CT for pelvic staging. Data on both clinical utility in standard care and cost-effectiveness will be required to change these recommendations.
standard external beam radiotherapy. This has been evaluated in patients with high-risk prostate cancer and shown to improve local control in patients with poorly differentiated tumours but not overall survival or recurrence-free survival. However, increased late radiation sequelae were recorded.

The addition of pelvic radiation to prostate radiation has been evaluated in a number of studies, with no demonstration of an added benefit but with increased toxicity. However, the use of 3D conformal shaping can provide a 'surgical template' for pelvic nodal irradiation and IMRT can permit substantially higher doses including boosts to be delivered while maintaining small bowel dose tolerances. This will underpin future pelvic radiotherapy trials.

Conventional radiation schedules range between 70 and 80Gy administered over 7–8 weeks. Studies have evaluated shorter radiation fractionation schedules (hypofractionation) on the radiobiological basis that the cellular sensitivity of prostate cancer may respond better to a larger dose per fraction than the conventional 1.8–2.0Gy per fraction with greater sparing of the normal tissues.

**Future directions in radiotherapy**

Pelvic organ movement around the prostate can be an issue in terms of accurate delivery of daily radiotherapy and it is known that a filled rectum or the bladder, to a lesser degree, can affect the location of the prostate. This issue could be minimised with the use of image guidance techniques that ensure reliable and accurate delivery of radiation either before or during treatment delivery. Recent reports using image-guided radiation therapy with IMRT have recorded significantly improved biochemical PSA control rates with less treatment toxicity, and this may become the standard of care in the future.

Other methods are being investigated to reduce radiation to dose-limiting normal structures such as the rectum. The insertion of ‘obturators’ or spacers such as gel (Augmenix) or a biodegradable balloon (ProSpace) is intended to minimise rectal motion and/or displace the rectum from the high-dose radiation regions around the prostate.

Another strategy to improve patient outcomes for localised high-risk prostate cancer is to target the dominant nodule within the prostate. There are many different methods to locate the dominant or functionally radioresistant nodule using multiparametric MRI or magnetic resonance spectroscopy, or $^{18}$F- or $^{11}$C-choline positron emission tomography (PET) scanning. By isolating the site of potential relapse, this region can be targeted and boosted with IMRT. Chang and associates confirmed the feasibility of IMRT dose painting using $^{11}$C-choline PET scans in patients with localised prostate cancer. This method has been modelled to provide good tumour control while minimising any late side-effects.

**Hormonal therapy**

Hormonal therapy has a major role in combination with radiotherapy in high-risk localised or locally advanced prostate cancer. Neoadjuvant hormonal therapy (NHT) given before definitive radiotherapy treatment can reduce tumour bulk and prostate volume; short-term therapy of 3–4 months was shown to reduce prostate size by 25–30%. The administration of NHT to reduce prostate gland size could also allow the application of more focused radiotherapy and potentially reduced toxicity to the surrounding normal tissues.

**Neoadjuvant hormonal therapy plus radiotherapy**

The role of NHT and adjuvant hormonal therapy (AHT) plus radiotherapy has been evaluated in depth by Payne et al. Overall, the addition of NHT and/or AHT has been shown to improve time to disease progression and/or overall survival.
compared with radiotherapy alone in high-risk localised and locally advanced prostate cancer. NHT is normally given as a short course of therapy, either 3 or 6 months. Reports indicate that intermediate-risk patients may also gain survival benefits from 4–6 months of hormonal therapy before and during radiotherapy.29,30

Adjuvant hormonal therapy plus radiotherapy
It has been established in a number of studies that AHT plus radiotherapy provides significant improvement in 10-year outcome. The seminal EORTC study by Bolla et al. reported that in patients with high-risk localised or locally advanced prostate cancer, the addition of ADT initiated at the start of radiotherapy and continued for 3 years significantly improved survival compared with hormonal therapy given to disease progression after radical radiotherapy (Figure 2).31 The study demonstrated an increase in 10-year overall survival from 39.8% to 58.1%. Other randomised phase 3 studies of adjuvant luteinising hormone-releasing hormone (LHRH) agonists have demonstrated similar very positive results and it is now standard practice to continue with hormone therapy for 2–3 years after radiotherapy.

The rationale for ADT alone as opposed to therapy in combination with radical radiation treatment has been investigated in two important studies. The SPCG-7 study randomised men with locally advanced prostate cancer to treatment with 3 months of total androgen blockage followed by continuous treatment with an LHRH agonist or the same treatment plus radiotherapy.32 Ten-year prostate cancer-specific mortality was 23.9% in the endocrine group and 11.9% in the endocrine plus radiotherapy group. The cumulative incidence at 10 years for PSA recurrence was higher in men in the endocrine-only group (74.7% versus 25.9%, p<0.0001). The MRC PR07/NCIC PC3 study reported by Warde et al. compared a similar regimen, using hormone therapy/orchiectomy with and without radiotherapy in men with T3/T4 N0/NX or T2 and PSA >40ng/ml or T2 and PSA >20ng/ml and Gleason score 8–10 prostate cancer.33 This reported 7-year overall survival rates of 66% for ADT alone versus 74% for combined treatment.

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