Understanding radiotherapy and its potential for use in novel combination trials

Prostate cancer

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UK incidence

Prostate cancer is now the most common male cancer in the UK (around 35,000 cases per annum) and the second most common cause of male cancer deaths (around 10,000 per annum; Cancer Research UK statistics, 2007).

Stage distribution at presentation and indications for radiotherapy

Localised disease occurs in 60% of patients at presentation and is defined as prostate cancer confined within the capsule of the prostate gland; locally advanced disease occurs in 30% and is defined as disease beyond the capsule but not metastatic beyond the pelvic lymph nodes.

Radiotherapy (external beam and brachytherapy) is the most frequently used curative therapy for localised and locally advanced prostate cancer in the UK. The generally accepted radical external beam dose in the UK is 74 Gy in 2-Gy fractions. Most patients are treated with neoadjuvant and concomitant hormone therapy, and high-risk cases may receive up to 3 years of adjuvant hormone therapy in addition. All patients should be treated using CT-planned 3-dimensional conformal radiotherapy. Intensity-modulated radiotherapy (IMRT) is now often used to treat the pelvic lymph nodes.

Radiotherapy is also used in the adjuvant and salvage settings post surgery. At least 3500 radical prostatectomies take place annually in the UK. With a tendency for surgeons to operate on more high risk cases, the number requiring adjuvant or salvage radiotherapy will also increase. In the palliative setting, radiotherapy (external beam and bone-seeking radionuclides) is commonly used to treat symptomatic bone pain secondary to metastases.

Low dose rate (LDR) permanent seed brachytherapy is now well established as a treatment for the treatment of low risk localised prostate cancer. The use of high dose rate (HDR) brachytherapy as a

boost to external beam therapy in high risk, localised disease is expanding despite the lack of randomised trial evidence of benefit. The complexity of radiotherapy use for prostate means that much of the ongoing research work is focussed on the technical aspects or prostate radiotherapy, and this is included in this review for completeness.

Prostate cancer biology

Almost all tumours are adenocarcinomas, which are graded using the Gleason scoring system. This can be combined with prostate-specific antigen (PSA) and T stage within nomograms to predict long-term outcome for any of the major treatment approaches, and has been reviewed recently in the context of external beam radiotherapy for localised disease (1). The most developed nomograms in patients managed by external beam radiotherapy have been developed by Kattan and colleagues; these have been shown to predict metastasis-free, cause-specific and overall survival better than the standard Radiation Therapy Oncology Group (RTOG) risk groups (2,3).The benefit of incorporating additional factors into nomograms is a topic of much research, with promise for histopathological features (number or percentage of positive cores, length of cancer within a core and presence of small volume 'tertiary' high grade disease) and biochemical features (PSA velocity/doubling time or PSA density) (4). There has been increasing interest in the potential of molecular markers to improve such nomograms as these may offer insight into the key biological processes. Interpretation of their importance is complex as much work relates to disease development, outcome following surgery or in the castrate refractory setting and may not be directly relevant for radiation oncologists. As always with prostate cancer, prolonged follow-up is necessary. Furthermore, radiotherapy is often given with short- or long-term androgen deprivation therapy (ADT) and long-term outcome may be dominated by androgen sensitivity.

However, the RTOG has done much work analysing two of their studies: RTOG 86-10 and 92-02, also recently reviewed by Roach (1). RTOG 86-10 compared the outcome of 456 men with locally advanced disease randomised to external beam radiotherapy (EBRT) alone or with 2 months of neoadjuvant and concurrent ADT (goserelin and flutamide) (5). RTOG 92-02 compared the outcome of 1554 men with locally advanced disease randomised to EBRT with 2 months of neoadjuvant and concurrent ADT (goserelin and flutamide) alone or with an additional 2 years of adjuvant goserelin (6). They have shown that the predominant pathways related to long-term outcome are proliferation (Ki-67 (7-9), protein kinase A RI-alpha (PKA) (7,10)), cell cycle (p53, p16 (11,12), MDM2 (13)), and apoptosis (Bcl-2 and Bax (7)).

Work from these trials has also shown an association between outcome and Cox-2 (inflammation and angiogenesis) (14), STAT3 expression (proliferation and apoptosis) (15) and subcellular Survivin expression (apoptosis and cell cycle) (16). Work from other groups is supportive for Bcl-2 (17), p53 (18), Ki-67 (19) and VEGF staining/HIF-1α expression (intrinsic markers of hypoxia and angiogenesis) (20) in the radical setting and for the apoptotic pathway in castrate-refractory disease (21). The importance of the androgen pathway has been emphasised by the emergence of the *TMPRSS2-ERG* gene rearrangement as an early step in prostate cancer development (22,23), which is present in patients with high grade prostatic intraepithelial neoplasia (PIN) and still present in intermediate risk patients (24). It has been shown to be associated with clinical outcome in some (25,26) but not

all studies (27), especially if there are increased copy numbers; the relevance for patients undergoing radiotherapy is presently unknown.

Research topics in prostate biology:

- Prognostic and predictive factors associated with tumour outcome after radiotherapy, e.g. the hypoxia pathway. Additional confounding factors include: use/duration of ADT, dose and fractionation schedule, radiation modality (IMRT, protons, LDR, HDR)
- Biological implications of different radiation modalities in particular advanced radiation techniques, e.g. bystander effect. Little is known about the optimisation of radiotherapy in terms of potential extra-tumour effects (28,29).
- Prognostic and predictive factors associated with normal tissue toxicity after radiotherapy, i.e. radiogenomics.

External beam radiotherapy for prostate cancer

Localised disease

It is not known whether the standard local therapies (radical prostatectomy, EBRT and LDR brachytherapy) are equivalent in terms of tumour control and long term survival, but they are generally assumed to be so. We are not yet able to identify with certainty which patients do not need radical treatment, but a consensus does exist on which patients should be considered for active surveillance (30). We also do not know which patients are best treated with the various modalities available.

Radical prostatectomy reduces disease-specific mortality, overall mortality, and the risks of metastasis and local progression compared to a watchful waiting policy (31). In external beam radiotherapy, dose escalation from 64 to 74 Gy in 2-Gy fractions improves PSA control and this has become standard UK practice. Further dose escalation is presently limited by late (rectal) toxicity, which was approximately doubled in the dose escalation trials (32). It is unknown whether any particular groups benefit more than others from dose escalation. Advanced delivery technology (IMRT, image-guided radiotherapy [IGRT]) offer the potential to reduce the level of normal tissue irradiation for a given level of target coverage and are thus being actively researched in the UK and beyond (CHHiP IGRT substudy). Optimisation of the dose fractionation schedule may also help (CHHiP), or be shown to be irrelevant, which may open the door for radical hypofractionation (as in breast cancer trials) and with the ongoing Scandinavian BeamCath study, which is examining a new device which allows better positional verification of the prostate during radiotherapy.

The use of hormone therapy with radiotherapy in prostate cancer

Strong evidence from randomised controlled trials supports the use of ADT with radiotherapy in the treatment of localised and locally advanced prostate cancer (33). Neoadjuvant ADT (given for 3–6 months prior to radiotherapy) improves overall survival in low grade cancers and biochemical and clinical disease-free survival in all tumour grades. Concomitant and adjuvant (1–3 years) ADT have been conclusively shown to improve overall survival in locally advanced and high grade prostate

cancers. A recent meta-analysis has confirmed the importance of hormone therapy with radiotherapy (33).

Standard treatment concepts in locally advanced disease

UK practice is generally to use long-term ADT with prostate and pelvic nodal radiotherapy e.g. the MRC STAMPEDE trial (PRO8), which is an ongoing phase III RCT which includes men with high risk localised or locally advanced hormone-naive prostate cancer randomising to hormone therapy alone (+ radiotherapy if appropriate) or one of 5 other arms which include zoledronic acid, docetaxel, celecoxib, or combinations of the above. Uncertainties include whether there is any benefit of pelvic nodal radiotherapy compared with prostate radiotherapy alone (being explored in the phase II PIVOTAL study), and the optimal duration of adjuvant ADT. The STAMPEDE trial will include a significant amount of men treated with radiotherapy for high risk localised disease.

With regards to radiotherapy in T3 disease, there are a number of current research questions including the role of brachytherapy in combination with external beam RT, and the role of surgery with planned post-operative RT.

Technology research opportunities with radiotherapy for prostate cancer

1. Functional imaging in prostate cancer radiotherapy

Standard local staging for prostate cancer includes trans-rectal ultrasound (TRUS) and/or pelvic MRI. Only 60% of prostate tumours are visible on ultrasound imaging and it is no more accurate in local staging than digital rectal exam (DRE) (34). 3D-US may be more accurate but is operator dependant (35). Compared to TRUS and DRE, MRI provides improved local staging with regard to extra-capsular spread and seminal vesicle involvement (36). Endo-rectal MRI may provide improved image quality over external coil MRI.

Routinely in radiation treatments the whole prostate gland is treated, but there is considerable interest in using functional imaging to target boost or focal primary/salvage treatments to areas of gross tumour within the prostate. Targeted treatments may improve local control and/or reduce morbidity.

There are a number of advanced MR techniques in development for functional imaging. Proton MR spectroscopic imaging can be used to differentiate between tumour and normal tissue by quantifying the concentration of metabolites such as citrate, choline, creatinine and polyamines within the gland (37). Diffusion-weighted MRI (DW-MRI) measures diffusion coefficients of biological tissues and dynamic contrast-enhanced MRI (DCE-MRI) quantifies tissue vascularity.

There are several studies that demonstrate functional MR imaging is a reliable means of identifying areas of the prostate involved with tumour and can be used to help target diagnostic biopsies (38-41). This is an active area of research but to date there are no published prospective studies using functional imaging to guide radiation treatments.

Nodal staging using MR or CT is standard in high risk prostate cancer. The decision on whether a node is involved or not depends solely on size criteria, leading to under-staging. High-resolution MRI with lymphotrophic ultra-small super-paramagnetic iron oxide particles (USPIO) may be helpful in the detecting small otherwise occult lymph node metastases (42,43).

Research topics in functional imaging:

- Identifying biological foci of radioresistant or micrometastatic disease to improve individualised therapy selection or to direct focal radiotherapy boosts using functional imaging, e.g. DCE-MRI to define hypoxic areas or ^{11}C-Choline PET . Using functional imaging, it may be possible to identify the dominant malignant area within the prostate gland and therefore deliver a higher dose of radiation to a small volume of the prostate.
- Improving technical aspects of target volume delineation during the radiotherapy planning process using, for example, MRI in radiotherapy planning. Traditionally, the volume of tissue to be treated with radiotherapy is delineated by a radiation oncologist on images obtained from a planning CT scan. It is now possible to combine information from MRI to give better anatomical definition of the tumour.

2. Focal treatments

Although prostate cancer is often multi-focal within the gland, there is evidence that metastatic disease is monoclonal and may develop from a single precursor cell within the prostate (44). It may be that the index lesion (the largest tumour focus in the prostate) dictates the risk of metastatic disease and survival. In lower risk patients, radiation treatments using brachytherapy or IMRT could be directed at the index or dominant lesion, thereby reducing morbidity without compromising cancer survival. In more high risk patients, boost doses of radiation could be delivered to these lesions.

Research topics in focal treatment include:

- Developing and comparing the various technologies that can deliver focal radio-ablative therapies and comparing with other ablative therapies (ultrasound, cryotherapy, etc.). There are a number of these type of non-radiotherapy modalities being tested and used clinically in localised prostate cancer. The most commonly used modality is high intensity focused ultrasound (HIFU). There may be opportunities to compare results of these technologies with radiotherapy. There is very little data on the use of these modalities in patients who have previously received radiotherapy.

3. Stereotactic treatments

Radiobiological modelling suggests the α/β ratio, quantifying fractionation sensitivity, for prostate cancer is low and there may be an advantage in delivering hypo-fractionated treatments. Developments in patient immobilisation and on-treatment imaging allow more accurate radiation delivery and facilitate stereotactic body treatments. For patients with early prostate cancer, stereotactic treatments are a more convenient non-invasive treatment option, and are less resource intensive for departments. Daily online image guidance can be used to ensure accurate treatment delivery using reduced margins. The existing published evidence base is limited to a small number of

single centre series with no more than 50 patients with localised disease (45,46). There is an ongoing multicentre Scandinavian RCT using 6.1 Gy x 7 fractions (HYPORT trial; 42.7 Gy total dose).

4. Image-guided radiotherapy

Technical developments now allow tracking of the prostate position throughout a 7–8 week course of radiation treatment. Daily image guidance can be used to correct for changes in prostate position, reducing the risk of geographical miss and allowing safe margin reduction. IGRT is resource intensive and the CHHiP IGRT sub-study is currently recruiting to assess the impact of daily image guidance with or without margin reduction, on acute and late toxicity.

Research topics in IGRT include:

- Developing and comparing the various technologies that can deliver IGRT, particularly exploring extreme hypofractionation with stereotactic EBRT solutions
- Incorporating functional imaging *during* radiotherapy and *adapting* original treatment based on observed response.

5. Brachytherapy

The combination of external beam radiotherapy and brachytherapy allows dose escalation over a shorter overall treatment time, delivering higher biological doses than achievable with external beam irradiation alone. A phase III randomised trial has demonstrated improved biochemical control using HDR brachytherapy boosts, with potentially less rectal toxicity than external beam radiotherapy alone (6,47), although the standard external beam radiation arm was not dose escalated. A number of different HDR dose schedules are used in clinical practice (48). A recent Canadian trial has demonstrated that a single HDR boost of 15 Gy can be delivered with no significant increase in toxicity (49). With the increasing availability of prostate HDR there is potential to carry out a randomised trial comparing dose-escalated external beam radiotherapy alone versus external beam radiotherapy and HDR brachytherapy.

In low risk prostate cancer, the disadvantage of HDR monotherapy as compared to permanent LDR brachytherapy has been the need to fractionate treatments, but studies suggest it may be possible to deliver HDR safely in fewer treatments (50) and it then becomes feasible to develop a phase II toxicity trial comparing LDR and HDR monotherapy.

Research topics in brachytherapy include:

- Comparing outcome of LDR with surgery and EBRT
- Comparing outcome of HDR with extreme hypofractionated IGRT .

Therapeutic opportunities with radiotherapy in prostate cancer

1. External beam radiotherapy in combination with other agents

ADT has already been shown to improve the outcome of many patients with prostate cancer receiving radiotherapy. The MRC STAMPEDE trial is presently exploring docetaxel, zoledronic acid and celecoxib in patients with locally advanced and metastatic prostate cancer (approximately 40%

are receiving radiotherapy). There are many other agents that could be combined with radiotherapy that might potentially improve outcome.

Possible approaches include:

- Hypoxia-targeting agents
- Additional hormonal agents
- Radioprotectors, either used for all patients OR selected patients based on risk of developing late rectal toxicity or following the development of acute rectal toxicity
- Agents targeting particular apparently relevant pathways: proliferation, cell cycle, inflammation, angiogenesis and apoptosis.

2. Immunobiology and radiotherapy

Almost uniquely in the spectrum of solid cancers, immunotherapy has been shown to improve survival in patients with metastatic prostate cancer, in a randomised clinical trial using ex-vivo treated dendritic cells to express tumour antigens (51). Prostate cancer can be considered a model system for immunotherapy, as the prostate is non-essential, malignant prostate cells express cell surface tumour antigens (prostate or cancer specific) and there is an inverse correlation between rates of cancer recurrence and numbers of infiltrating T-cells within tumour tissues, suggesting a role for host T-cells in controlling tumour growth (52). Radiotherapy causes a pro-inflammatory extracellular environment and mechanisms of radiation-induced cell death (whether apoptotic or necrotic) is immunogenic (53). Trials of a priming vaccine with recombinant vaccinia (rV) PSA plus rV containing the T-cell co-stimulatory molecule B7.1, followed by monthly booster vaccines with recombinant fowlpox PSA prior to radiotherapy, has been trialled by the National Cancer Institute (54,55). The initial results are encouraging as the T-cell responses generated prior to radiotherapy are not adversely affected by the radiotherapy, and if anything increased. ADT is also immunogenic and results in a huge influx of T-cells and antigen-presenting cells into the prostate within a few weeks (56).

Research topics in immunobiology include:

- Will the combination of immunological therapies safely improve the outcome of patients having radiotherapy (with any radiation modality)?
- What influence does ADT have on immunotherapy combined with radiotherapy?
- What is the optimal timing of immunotherapy with (ADT and) radiotherapy?
- Which immunotherapy approach is most efficacious/least toxic?

3. Bone-seeking radionuclide therapy in metastatic prostate cancer

Bone-seeking radionuclides including Strontium-89 and Samarium-153 EDTMP have been used in the treatment of painful prostate cancer bone metastases for almost 20 years (57-59). Recently, combinations of these agents with cytotoxic chemotherapy have shown promise in extending survival (60). A global phase III trial of the alpha-emitting radionuclide Radium-223 is nearing completion. This agent has a lot of potential for combination studies due to the low complication rate.

Research topics include:

- Choice of radionuclide – beta versus alpha emitter. This refers to the type of radiation emitted by the radionuclide. Beta emitters (e.g. Strontium-89) are the most well established agents and have a relatively long range of therapy in the order of a few millimetres. Alpha-emitters (e.g. Radium-223) have a very short range of radiation in the order of a few cell diameters.
- Combination therapy, e.g. Ra-223 + Sm-153/Re-188. Because of the different ranges of the radiation emitted by these agents, there may be a role for combination of beta and alpha-emitting radionuclides.
- Individualised prescribing: Most radionuclides in metastatic prostate cancer are prescribed per kg. There may be a benefit in using patient-specific factors e.g. renal function, alkaline phosphatase levels to better individualise the actual radiation dose received by the tumours.
- Dosimetry study: There is very little data on the actual dose received by individual metastases from bone-seeking radionuclide therapy in prostate cancer. Physics-based studies are warranted to get a better understanding of the distribution of radiation within a given patient.
- Combination of bone-seeking radionuclide with other agents:
    - Chemotherapy + repeated radionuclide therapy
    - Radionuclide + immune modulator (e.g. ipilimumab)
    - Radionuclide + poly (ADP-ribose) polymerase (PARP) inhibitor.

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