Radiotherapy of prostate cancer

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Radiotherapy is used for all stages of prostate cancer from early localised disease to locally advanced as well as metastatic stages. The method of radiotherapy used is dependent on the stage of the disease and is guided by the application of prognostic factors or disease groupings such as the NCCN classification [1,2]. In general, localised disease can be treated by either brachytherapy or external beam radiotherapy (EBRT), with EBRT being used for more advanced disease stages. Historically. in men with locally advanced prostate cancer, either expectant therapy or androgen deprivation therapy (ADT) alone have been used to manage or treat these cases. However recent randomised trials that compared the addition of radiotherapy to ADT versus ADT alone have reported an overall survival advantage for combination therapy [3,4]. More recently, the combination of both brachytherapy and EBRT or high-dose rate brachytherapy monotherapy are being used to treat intermediate to advanced stages. For metastatic disease, both EBRT and isotope therapy have been used successfully to ameliorate and control symptomatic disease.

Over the past decades, there have been substantial technological developments in radical radiotherapy with shaping of the treatment beams for conformal radiotherapy (CRT) and the ability to vary dose intensities within treatment fields for intensity-modulated radiotherapy (IMRT) [5]. In addition, multi-modality imaging, particularly with magnetic resonance imaging (MRI), functional MR such as spectroscopy and positron emission tomography (PET) has aided target volume delineation to ensure adequate coverage of disease and an opportunity to retarget biological radioresistant disease [6].

The use of CRT has been shown in a randomised trial to significantly reduce the incidence of clinically relevant rectal proctitis and bleeding (RTOG Grade $\geqslant$2) for the CFRT arm compared with conventional radiotherapy (5% vs. 15% respectively, $P = 0.01$) without any loss of PSA control [7] and established CFRT as the minimum standard for radical therapy. Subsequently, both CRT and IMRT have allowed the dose to be increased whilst respecting dose tolerances of the adjacent organ-at-risk (OAR), especially the rectum being the major dose-limiting structure.

A dose–response relationship has been demonstrated by several randomised trials. The results of these dose escalation studies for non-metastatic prostate cancer using mainly CRT are listed in Table 1 [8–14]. More recently a meta-analysis [15] confirmed that an increase in radiotherapy dose from 70 Gy to 80 Gy results in an increase in biochemical prostate specific antigen (bPSA) control rates by approximately 19% in patients with intermediate to high-risk prostate cancer [15].

Despite optimising CFRT techniques [16–18], the degree of dose escalation is limited as CRT is unable to spare the rectum if it lies within the concavity of the planning target volume [19]. This physical limitation will technically limit the degree of dose escalation possible with CRT. This is clearly demonstrated by the toxicity noted in the dose escalation trials outlined in Table 1, with the incidence of late GI toxicity (RTOG grade $\geqslant$2) being doubled by dose escalation to 74–78 Gy. Whilst most of these randomised trials have used CRT, the Massachusetts General Hospital (MGH) study used protons to deliver the escalated dose [11]. Although proton therapy may potentially provide a technically improved dose distribution through manipulation of the Bragg peak dose deposition, the toxicity reported in the escalation arm was similar to that of other studies.

It was expected that the ability to vary the dose fluence over treatment fields using IMRT can substantially improve dose conformity and OAR avoidance. In the large prospective non-randomised series from the Memorial Sloan Kettering Cancer Centre, both acute and late toxicities were substantially reduced, even when escalating dose to 81 Gy and 86.4 Gy with late 3-year actuarial $\geqslant$ Grade 2 GI toxicity for this series of 772 cases being calculated at 4% [20]. A recent update with 10-year outcomes reported that the 10-year likelihood of developing grade 2 and 3 late GI toxicity was 2% and 1% respectively [21].

Table 1

Site [ref.]	No. of patients	5Y bPSA control		Late GI toxicity (RTOG ⩾2)	
		Standard (dose)	Escalated (dose)	Standard	Escalated
MDACC[a] [8,9]	301	64% (70 Gy)	70% (78 Gy)	8%	17%
RMH [10]	126	59% (64 Gy)	71% (74 Gy)	11%	23%
MGH [11]	394	61% (70.2 GyE)	80% (79.2 GyE)	12%	26%
Dutch [12,13]	664	54% (68 Gy)	64% (78 Gy)	16%	21%
GETUG [14]	306	68% (70 Gy)	76.5 (80 Gy)	14%	19.5%

[a] 6 year bPSA rates. GyE = Gray equivalent.

The treatment of pelvic nodal volumes remains controversial. The RTOG 94–13 trial initially suggested that intermediate- to high-risk prostate cancer subsets might benefit from pelvic nodal irradiation [22]. However, a later report did not demonstrate any biochemical PSA control benefit [23]. A similar non-beneficial outcome was reported from the French study for treatment of pelvic nodes in men with more advanced prostate disease [24]. This therapeutic question will soon be studied within a United Kingdom randomised study. If pelvic volumes are being irradiated, then the use of IMRT can substantially reduce the dose to the bowel when treating surgical template nodal volumes and may also permit dose escalation to the nodal regions with acceptable toxicity [25].

The use of post-operative radiotherapy following radical prostate surgery has been demonstrated to provide up to 20% bPSA relapse-free survival in three randomised studies compared with a 'wait and see' policy [26–28]. The main benefit is for men suffering from positive margins and pT3 disease. In a recent report, the South West Oncology Group (SWOG) published an overall survival benefit with post-operative radiotherapy. There is an ongoing study evaluating the use of adjuvant versus delayed prostate bed radiotherapy as well as an evaluation of the use of ADT and its duration of use [29].

More recently, the use of large dose per fraction or hypofractionation has generated much clinical interest. The radiobiological rationale is that prostate cancer cells may have a low α/β ratio around 1.2–1.5 Gy [30] and this implies that a larger dose fraction may improve the therapeutic ratio. Recent studies using 2.63 Gy to 3.13 Gy daily dose fractions to total doses of 50 Gy to 55 Gy have reported rates of late bowel toxicity comparable with those of conventional dose schemes [31–34]. In addition, biological dose escalation using hypofractionation may also increase local control rates with acceptable complication rates. This has been explored by several groups throughout the world with reports in abstract form of acceptable acute toxicity.

A crucial issue for any precision radiotherapy, particularly CRT or IMRT, is to account for any daily displacement of the target during radiotherapy in order to avoid a geographical miss. Internal pelvic motion such as rectal distension can cause displacement and/or deformity of the prostate gland from its planned 3D location, as defined on the radiotherapy treatment scan. This can cause both systemic and random errors in treatment delivery to the perceived 3D prostate position. Reviews of these potential errors have confirmed reduced local control outcomes, with a loss of bPSA control rates for these patients that is approximately equivalent to the escalated dose [35,36]. A variety of methods have been devised to combat these issues of temporal spatial uncertainty by using adaptive radiotherapy (ART) or image-guided radiotherapy (IGRT) strategies. ART strategies include using bounding target or average prostate volumes using information gleaned from 4–5 pelvic scans performed before or during the first week of radiotherapy. These methods have been demonstrated to reduce treatment volumes by up to 40% and appropriate dose escalation with acceptable early outcomes. Other online methods include daily prostate localisation with in-room stereotactic ultrasound systems or online imaging using linear accelerator attached cone beam systems for cross-sectional imaging and fiducial markers with stereoscopic CCD cameras. Systems such as the Cyberknife, capable of online tracking for IGRT, are now in routine use.

Future directions include the use of these IGRT techniques to permit targeting of functional volumes. Clinico-pathological studies have confirmed the correlation of MRI or choline PET leading to the boosting of the dominant intra-prostatic nodule to doses up to 90 Gy [37], and early feasibility clinical studies have been undertaken with acceptable acute toxicity [38]. Very large dose per fractions up to 6–8 Gy are also being investigated with extra-cranial stereotactic body

techniques together with the combination of high-dose rate brachytherapy. All these technical advances have the potential to improve patient outcomes with prostate radiotherapy and needs proper evaluation within randomised comparative studies to fully quantify the benefits.

Conflict of interest statement

The author has disclosed no conflict of interest for this body of work.

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