Localised prostate cancer – new surgical and radiation techniques

Radical radiotherapy – Techniques, results and side effects (evolving tools in definitive radiotherapy, intensity modulated radiotherapy, image guided radiotherapy and their role in dose escalation)

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External beam radiotherapy (EBRT) has been used extensively for early localised and locally advanced prostate cancer (PC). EBRT has undergone substantial changes due to technical developments in equipment and techniques that have permitted treatment fields shaping with conformal radiotherapy (CFRT) and improved dose distributions using intensity modulated radiotherapy (IMRT) [1]. These advances have allowed dose increases whilst respecting dose tolerances for adjacent normal pelvic tissues, particularly the rectum being the dose limiting organ-at-risk (OAR).

The rationale for dose escalation in PC stemmed from USA Patterns-of-Care studies suggesting better disease-free intervals with higher EBRT doses, particularly for locally advanced subsets. However, using conventional EBRT or unshaped treatment fields, relatively modest increases in dose from 60 Gy to above 64–66 Gy resulted in substantial increases in rectal toxicity from around 6–10% to 11–20% [2–4]. These side-effects negate the potential benefit of attempting dose escalation using conventional EBRT.

The value of field shaping to the profile of the prostate target has been examined. The Royal Marsden Hospital (RMH) randomised trial reported a significant reduction in the incidence of clinically relevant rectal proctitis and bleeding (RTOG Grade $\geqslant 2$) for the CFRT arm compared to conventional radiotherapy (5% versus 15% respectively, $P = 0.01$) without any loss of PSA control [5] and established CFRT as the new standard technique.

Dose escalation CFRT trials in clinically localised PC are shown in Table 1. The MD Anderson Cancer Centre (MDACC) trial reported the 6Y-biochemical (b)PSA control rates that favoured the 78 Gy arm ($P = 0.03$) with greatest benefit for men with pre-treatment PSA > 10 mg/ml [6]. The RMH study suggested that the 74 Gy arm had better actuarial 5Y-bPSA control rates [7] and merged into the UK-RT01 study now completed with over 850 patients. The Massachusetts General Hospital (MGH) study used protons to deliver the escalated dose with improved 5Y-bPSA control rates for the escalated dose ($P < 0.01$) noted in all subgroups [8]. The Dutch trial also reported a benefit for the escalation arm ($P = 0.2$) [9]. Despite optimisation of CFRT techniques, the degree of dose escalation is limited as CFRT cannot spare the rectum if it lies within

Table 1
Dose escalation CFRT trials in clinically localised PC

Site [ref.]	No. of patients	5Y bPSA control		Late GI toxicity (RTOG $\geqslant 2$)	
		Standard (Dose)	Escalated (Dose)	Standard (Dose)	Escalated (Dose)
MDACC [6][a]	301	64% (70 Gy)	70% (78 Gy)	8	17
RMH [7]	126	59% (64 Gy)	71% (74 Gy)	11	23
MGH [8]	394	61% (70.2 GyE)	80% (79.2 GyE)	12	26
Dutch [9]	664	54% (68 Gy)	64% (78 Gy)	16	21
GETUG	306	TBA (70 Gy)	TBA (80 Gy)	TBA	TBA

No. Pts = number of patients; GyE = Gray equivalent; TBA = results to be announced.
[a] 6 year bPSA rates.

the concavity of the target volume [1]. This physical limitation restraints the extent of dose escalation possible with CFRT. Dose escalation trials outlined that the incidence of late GI toxicity (RTOG grade $\geqslant$2) is roughly doubled by dose escalation.

IMRT can provide better dose conformality and OARs avoidance as demonstrated in the prospective non-randomised Memorial Sloan Kettering Cancer Centre IMRT series of 772 localised PC cases [10]. 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 group being 4%. The RTOG 94-13 trial suggests that intermediate to high risk prostate cancer subsets may benefit from pelvic nodal irradiation [11]. IMRT can be used to reduce dose to bowel when treating surgical template nodal volumes and may also permit dose escalation to the nodal regions with acceptable toxicity.

More recently, hypofractionation has generated much interest with the radiobiological inference that prostate cancer cells may have a low α/β ratio around 1.2–1.5 Gy [12] and thus larger dose fractions may improve the therapeutic ratio. Recent studies using 2.63 Gy–3.13 Gy daily dose fractions to total doses of 50 Gy–55 Gy have reported comparable rates of late bowel toxicity to conventional dose schemes [13–15]. In addition, hypofractionated dose escalation 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.

Another important issue for precision CFRT or IMRT is internal pelvic motion such as rectal distension which can cause displacement and/or deformity of the prostate gland from its perceived spatial position. This can cause a systemic error in the prostate location and result in a geographical miss for treatment delivery with reduced bPSA control rates for these patients [16]. A variety of image guided methods have been developed to combat issues of temporal spatial uncertainty in prostate radiotherapy such as online 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 for adaptive radiotherapy or gated image guided radiotherapy (IGRT). All these technical advances have the potential to improve patient outcomes in prostate radiotherapy.

Conflict of interest statement

None declared.

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