**IMRT for prostate cancer**

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**Introduction to prostate cancer**

The increased frequency of PSA testing has led to an increased diagnosis of early organ confined prostate cancer. Diagnosis is primarily made by histology, via TRUS-guided sextant biopsy or template biopsy which can provide improved localisation of cancer within the prostate. Staging is from digital rectal examination, from imaging with multi-parametric MRI (TNM staging), from PSA levels, and from histology (Gleason score). Those with localised disease have radical treatment options, primarily surgery with radical prostatectomy +/- lymph node clearance or radical radiotherapy, which can be delivered by external beam radiotherapy (EBRT) or by interstitial radiotherapy (brachytherapy). Most patients undergoing radiotherapy have EBRT. Those with minimal urinary symptoms and low risk disease may be eligible for low dose rate brachytherapy, and those with localised bulky tumour may be eligible for high dose rate brachytherapy in combination with EBRT. In the UK in 2014/15, 15,868 patients received radical prostate radiotherapy, of which 1,504 were brachytherapy.

**Radiotherapy and features of IMRT**

Radiotherapy aims to damage double-stranded DNA of clonogen cells by using ionising radiation, causing aberrations and mitotic cell death. The treatment volume includes the gross tumour volume (GTV), a margin around this to allow for microscopic spread (clinical target volume or CTV) and an additional margin for internal movements of the organ between planning and treatment or during treatment (planning target volume or PTV). The irradiated volume will invariably include some adjacent normal tissues and result in toxicity. The severity and type of these side effects vary according to type of tissue, dose and volume treated.

Three-dimensional conformal radiotherapy planning (3DCRT) consists of using CT imaging to define treatment targets to which radiation is delivered by using uniform beam intensities. Intensity modulated radiation therapy (IMRT) is an advanced form of 3DCRT, whereby the intensity across the individual radiation beams can be varied, allowing a pre-specified dose range to be delivered to certain volumes such as the tumour or the normal tissues around it (figures 1 and 2). IMRT planning can produce concave shaped isodose distributions which are not possible with 3DCRT, allowing more accurate conformity to irregularly shaped planning target volumes while avoiding or at least limiting the dose to normal tissues such as the rectum, bowel, urethral bulb and bladder. Lower complication rates improve quality of life and reduce costs of patient care following treatment.

With the high conformity and steep dose fall-offs achieved with IMRT, it is imperative to deliver each treatment fraction accurately. Movements of the prostate are very common and unpredictable, mostly from changes in rectal volume (gas or solids) and bladder filling (figure 3). In addition, muscular tension in the buttocks can move or rotate the whole pelvis. A shift of the delivered radiotherapy dose into normal tissues reduces efficacy and increases toxicity, for example to the rectum. These shifts can be corrected by imaging the prostate and adjusting the couch position before each treatment. One option uses small gold (fiducial) markers which are inserted into the prostate, similar to a transrectal biopsy, prior to image guided radiotherapy (IGRT) planning. Other methods include cone beam CT scanning, CT on rail scanning, or ultrasound localisation. Procedures to reduce changes in pelvic anatomy (diet, rectal mini-enema rectal balloon, or a drinking protocol) may also improve treatment accuracy.

**Routine clinical practice**

New patients eligible for either surgery or radiotherapy options are often seen in the joint uro-oncology clinic where the possible treatment modalities are discussed. Treatment recommendations depend on the staging, the comorbidities and the general fitness of the patient. NCCN definition is the commonest classification used in the UK. Patients with low risk disease are normally offered active surveillance with repeated PSA tests, MRI scans and, if indicated, repeated prostate biopsies. Patients with intermediate and high risk localised disease are treated with six months or three years of androgen deprivation therapy. Intermediate risk patients receive radiotherapy to the prostate only, while higher risk patients may also receive radiotherapy to the pelvic lymph nodes. The patient receives around three months of hormone therapy before radiotherapy; this avoids a volume reduction during the radiotherapy course and allows a smaller target volume and hence reduced toxicity. Fiducial marker insertion (three gold markers) is ultrasound-guided under a local anaesthetic with antibiotic cover. This is performed a couple of weeks before the radiotherapy planning scan in case of shifts before radiotherapy planning. Prior to the planning CT scan, bowel and bladder preparation is performed depending on the local protocol. A dedicated wide bore CT scanner with a flat-topped couch allows for positioning of the patient with ankle stocks and knee support as they will be throughout treatment, and small permanent skin tattoos are created over the reference markers that correspond to the lasers beam markers. This will allow the patient to be positioned for each treatment in the same way relative to the linear accelerator by aligning the fixed lasers with the tattoos. Radiotherapy planning will then occur over the next few days, with the patient starting treatment around one to two weeks after the planning appointment.

**Prostate IMRT planning**

In standard practice, the tumour volume (GTV) is not individually delineated as it is not readily identifiable. Also because of the multifocal nature of prostate cancer, the treatment volume includes the whole prostate. Depending on the patient’s individual risk category, varying amounts of the seminal vesicles or the pelvic nodal volumes are included in the clinical target volume (CTV). Delineation on CT imaging can lead to over- or underestimation of the volume as border definition can be difficult, especially at the apex. Hence, disease features on the staging multi parametric MRI should be noted while performing delineation, or even co-registra-
tion of a planning MRI to the planning CT to improve outlining accuracy. Normal structures are also delineated, including bladder, rectum, small and large bowel, femoral heads, urethra, and urethral bulb (figure 4). Increasing radiation doses and volume are associated with rectal, bowel or bladder, and erectile dysfunction. Prostate planning is dose-volume based. Dose-volume histograms provide visual representations of the dose received by the treatment volumes and organs at risk.

The size of the margin from CTV to PTV is dependent on the treatment IGRT protocol. With daily on-board pretreatment imaging using fiducial markers, this margin can be significantly reduced. Prostate IMRT is delivered with static fields, normally 5 or 7. An alternative is rotational IMRT, whereby a single beam of continually varying shape rotating around the patient, providing a faster delivery time (around 4-5 minutes for one arc) compared to static IMRT. This requires a rigorous quality assurance programme.

There are ongoing studies on optimising dose fractionation schedules. Oncology centres may vary in their practice, but generally acceptable regimens include 74-78 Gy in 37-39 fractions over 7.5-8 weeks. There is increasing evidence that delivering higher doses per fraction (ie hypofractionation) may be beneficial for prostate cancer treatment. Results from a large UK led trial (CHHiP) demonstrated that for intermediate risk prostate cancer, 60Gy in 20 fractions have equivalent effectivity and low toxicity rates.11

Acute and late toxicities

Early toxicity may include fatigue, nausea, erythema, urinary (dysuria, frequency, nocturia, incontinence, urgency, haematuria) and bowel (diarrhoea, bleeding, mucositis) symptoms. Serious late complications include haematuria, urinary incontinence, erectile dysfunction, rectal bleeding and bowel incontinence. Mature follow-up data have shown a significant reduction in grade 2 rectal complications with IMRT, although less so for urinary complications.12

Management after radiotherapy

Following this treatment, patients are monitored primarily by clinical assessment and PSA blood tests. If the patient is on hormone therapy, the PSA should remain suppressed. Once the hormone therapy is stopped, the PSA would naturally rise to a nadir level around 6-18 months after hormone cessation. A biochemical relapse is defined by further PSA increase to nadir level +2 (µg/l). Patients with intermediate or high risk disease have biochemical free survival of approximately 88% and 80% at five years.13 Even with relapsed disease, patients can survive for many months.

Future direction with IMRT

Traditionally, the aim of radiotherapy treatment has been to deliver a homogenous dose to the target volume. With improving technology and understanding of radiobiology, there is growing interest in dose painting radiotherapy, whereby dose escalation can be achieved to specific sections of the target volume such as areas of tumour on the staging MRI scan or choline PETCT scan. For prostate cancer at our centre, we have an ongoing phase II clinical trial (BIO-PROP20 study, NCT02125175) where patients receive 60Gy in 20 fractions to the target volume with dose escalation to 68Gy for tumour nodules. The rationale is that clonogen cells density would be expected to be highest at these regions, and hence would benefit from a higher radiation dose.

Conclusion

Alongside surgery, radiotherapy remains an important treatment modality for curative management of prostate cancer. Technological advances have significantly improved dose delivery to the target while minimising dose to adjacent normal tissues, and this has led to the increasing importance of accurate target delineation. It remains a well-tolerated treatment and, in the future, further improved clinical outcomes will hopefully be realised when the results of trials on dose-fractionation schedules and dose-escalation are mature.

References

Figure 3
Changes in faecal loading can affect prostate position and rotation (left: planning MRI; right: planning CT).

Figure 4
Outlines of target volume and organs at risk.