IMPROVING PROSTATE BRACHYTHERAPY BY DEVELOPING IMAGE GUIDANCE

Peter L. Acher, Prokar Dasgupta and Rick Popert

Department of Urology, Guy’s & St Thomas’ NHS Foundation Trust, Kings College London School of Medicine, London, UK

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INTRODUCTION

Brachytherapy is a form of radiotherapy in which radioactive sources are positioned in or close to a tumour. By delivering radioactivity from the ‘inside out’ with a sharp decline in dose, targeting is far more specific to the intended treatment zone than traditional external beam methods. The corollary is that high doses can be given safely to the tumour without unnecessarily over-irradiating the surrounding organs at risk and causing subsequent morbidity.

There has been interest in applying these principles to prostate cancer for almost a century, and in the 1970s radioactive sources became available as sealed sources known as ‘seeds’. Modern isotopes include palladium-103 and iodine-125. Typically, 80 seeds (each slightly smaller than a grain of rice) are permanently inserted into and around the prostate, creating a local ‘cloud’ of radiation, the aim being to encompass the entire gland.

The long-term results of implantation when applied as an open retropubic method were unsatisfactory [1], largely due to an inability to position the seeds homogeneously. However, the development of TRUS in the 1980s allowed visual guidance of seed placement via a transperineal approach [2]. Contemporary results give an efficacy of permanent prostate brachytherapy for localized prostate cancer similar to that from radical surgery and external beam radiotherapy [3].

The key to success is to position the seeds appropriately. A dosimetric study after implantation, with information on the distribution of sources, provides technical feedback to the brachytherapist and assesses the quality of the implant. As it can take up to 2 years for a measurable biochemical response to the treatment (PSA nadir), an earlier analysis is reassuring to both patient and physician; if an implant is unsatisfactory, with ‘cold spots’, further treatment can be applied.

Historically the total dose of the implant corresponded to tumour response. Plain X-rays were also used to calculate the ‘matched peripheral dose’. This assumed that the calculated isodose volume (from the seed positions) equaled that of an ellipsoid of the same dimensions as the target. It also assumed that the prostate (not visualized on plain radiography) was in the same place as the seeds. Not surprisingly, this method was later found to be inaccurate [4].

CT-based dosimetry developed alongside US-guided transperineal brachytherapy and is carried out in present practice for postoperative evaluation [4]. Soft-tissue structures are outlined on sequential CT axial scans and seed positions marked either manually or with the help of computerized automation. Computer software then interpolates between the slices and calculates the isodose contours. A three-dimensional (3D) rendering is presented providing easily interpretable analysis (see Figs 1 and 2).

Post-implant data from large series provided valuable information on optimal dosing and reduction of morbidity. By comparing dosimetric variables with tumour control and morbidity outcomes, optimal doses were defined [5]. The D90, or dose to 90% of the prostate, has been identified as the most predictive factor of outcome in terms of biochemical-free survival. However, the D90 is only a compromise; logically it would be expected that the D100 (dose to 100%) of the prostate would be more significant. The reason why it is not is that outlining the prostate on CT images is highly variable, due to the similar appearances of prostate and the surrounding venous plexus and pelvic floor musculature.

To try to improve dosimetry, other imaging methods have been tested. MRI provides better soft-tissue delineation than CT, but seeds give little or no signal, making distinctions between them and blood vessels, or defining them as near the rectal wall, difficult [6]. CT-MRI fusion is another option, matching bony and soft-tissue landmarks, and overlaying images to take advantage of the soft-tissue definition of MRI and seed locations from CT [7]. However, the patient must move between the two methods, causing anatomical movement of structures. Also, seed location on CT images is not entirely satisfactory; prostatic calcification gives similar appearances and seeds in clusters can be difficult to identify individually.

Plain X-ray films are optimal for imaging seeds, but necessitate 3D reconstruction. Fusion with MRI has been carried out by reconstructing 10 seed positions [8]. This method does not appear to have translated into common practice, probably due to the inherent difficulties in manually matching the 10 points between X-ray and MRI.

An alternative imaging method from the field of cardiothoracic surgery might hold the key to improving dosimetry [9]. The ‘XMR’ combines X-ray fluoroscopy with a horizontal-bore MRI scanner. The two are connected by a sliding table, thus minimizing patient movement between them. The table and the C-arm are both optically tracked using infrared light-emitting diodes, allowing a novel way of registering the two methods together. Although these machines are currently expensive, they are becoming more widely available.

At the same time, computer software has developed to such an extent that the implant can be planned during surgery. As the implant progresses, a real-time dosimetric assessment is made, based on seed deposition as seen on TRUS. This means that before the patient leaves the operating theatre, the treating physician can be satisfied with the implant; if unsatisfactory, more seeds can be positioned appropriately [10]. A further scan after the implant provides quality assurance.

The perfect prostate brachytherapy implant would target adequate radioactivity to cure the cancer whilst sparing the surrounding structures. Improved precision with modern developments in imaging are bringing us closer to this goal.
FIG. 1.
A transaxial MR slice of the prostate. Sources are shown in green. The prostate (red), rectum (blue) and urethra (dark green) are outlined. The light green, yellow and purple lines signify 145, 218 and 290 Gy isodose contours.

FIG. 2.
3D rendering of the implant.
The role of tamoxifen in reducing bicalutamide-induced gynaecomastia and breast pain

Martin C. Nuttall, James P. Harris and Guy P.C. Dawkins

INTRODUCTION

Gynaecomastia and breast pain are troublesome side-effects often experienced by men receiving hormonal therapy for prostate cancer [1]. Bicalutamide (Casodex®, AstraZeneca) is a nonsteroidal antiandrogen used in the treatment of prostate cancer, particularly in men trying to avoid some of the consequences of castration. The most common side-effects attributed to bicalutamide are gynaecomastia and breast pain, which are reported in over half of patients [2,3]. Gynaecomastia and breast pain often resolve on cessation of bicalutamide, but this might depend on the duration of therapy, as in one study gynaecomastia resolved in 64% of those taking bicalutamide for <6 months, but in only 29% of those taking it for >18 months [4]. This might be explained by the development with time of irreversible fibrotic changes within the breast tissue. Prophylactic breast irradiation has been used successfully to treat antiandrogen-induced gynaecomastia. For instance, in one study the incidence of gynaecomastia in men taking an antiandrogen for locally advanced prostate cancer treated with radiation was 28%, compared to 71% in those who did not receive radiation [4].

The development of gynaecomastia is thought to relate to an imbalance in the ratio between oestrogens and androgens, although in many cases the cause is often unknown and in others might be associated with a degree of hypogonadism [1]. The increased testosterone levels usually seen in men on antiandrogen monotherapy are thought to be the reason for the development of gynaecomastia. These can lead to a rise in the level of 17β-oestradiol secondary to androgen aromatization. These elevated oestrogen levels cause an irreversible benign proliferation of male breast tissue, perpetuated by the blockade of inhibitory androgen activity at the breast-bud [5]. Disrupting this process provides a rationale for preventing bicalutamide-induced breast pain or gynaecomastia, either by directly blocking the effect of oestrogen at a cellular level or by interfering with the peripheral aromatization of testosterone. Preliminary data showing a role for tamoxifen (Nolvadex®), AstraZeneca) in treating hormone-induced gynaecomastia and breast tenderness were first published in 1997 [6]. More recently, several randomized studies examined the effect of tamoxifen, an anti-oestrogen, and anastrozole (Arimidex®, AstraZeneca), a selective aromatase inhibitor, in preventing these side-effects.

Boccardo et al. [7] randomized 114 men with either localized, locally advanced or biochemically recurrent prostate cancer to bicalutamide plus either placebo, tamoxifen (20 mg/day) or anastrozole (1 mg/day) for 48 weeks. The endpoints of the study were the incidence of breast pain and gynaecomastia, serum PSA level, and sexual functioning scores. They found that the incidence of gynaecomastia was 73%, 10% and 51% in the placebo, tamoxifen and anastrozole groups, respectively; similarly, the respective incidence of breast pain was 39%, 6% and 27%. Adverse effects occurred in 37%, 35%

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Correspondence: Peter L. Acher, Department of Urology, 1st Floor, Thomas Guy House, Guy’s Hospital, St. Thomas’ Street, London SE1 9RT, UK.
e-mail: pete_acher@hotmail.com

Abbreviations: 3D, three-dimensional.

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