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The current role of imaging for prostate brachytherapy

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Abstract

Prostate brachytherapy is a radiotherapy technique for early stage prostate cancer that uses imaging guidance to place radioactive sources directly into the prostate gland. Transrectal ultrasound is used to facilitate a template-guided transperineal approach to the prostate and permits a highly conformal method of prostate radiotherapy with doses far higher than can be achieved with other radiation techniques. Maturing data has validated this technique as an acceptable treatment option with favourable and durable biochemical outcomes. The radiologist has a major role to play in the process: patient selection, guiding source delivery and follow-up after treatment all require close collaboration with colleagues in Radiation Oncology and Medical Physics. This review emphasises the specific contribution of imaging in the context of currently reported outcomes data.

Keywords: *Prostate; brachytherapy.*

Introduction

In recent years, there have been significant improvements in the management of localised prostate cancer but the optimal treatment remains undefined. There are a number of effective treatments available and different studies have reported that, for particular groups of patients, observation, surgery, radiotherapy, cryotherapy, or hormonal manipulation may all be appropriate and effective. In the absence of prospective clinical trials, survival and biochemical control data are difficult to assess and quality of life issues have consequently gained increasing importance in the choice of interventional therapy for individual patients.

Radiotherapy for prostate cancer can be delivered in different ways: conventionally, using external beam techniques or by implanting the radioactive sources directly into the prostate (brachytherapy). Prostate brachytherapy is not a new concept: various different radioactive sources have been implanted into the prostate using both open perineal and retropubic implant techniques as long ago as 1914. However, it was the introduction of newer isotopes such as iodine-125 and the development of transrectal prostate ultrasound that led to renewed interest in brachytherapy for prostate

cancer in the 1980s[1]. Transrectal ultrasound guidance facilitated a closed percutaneous transperineal approach to the prostate for source placement and the simultaneous development of sophisticated radiation planning software allowed much more accurate source placement and dosimetry. Continuing refinements in radiotherapy treatment planning techniques as well as technical advances in ultrasound have further generated the resurgence of enthusiasm for using prostate brachytherapy to treat clinically localised prostate cancer. In recent years, the reported series have confirmed that it is an effective treatment with high patient acceptability and morbidity outcome data. Prostate brachytherapy delivers a high dose of radiation to a very small target volume and hence there is very little unnecessary irradiation of adjacent bowel and bladder. It is also given as a single treatment and therefore has significant advantages in terms of logistics and patient convenience.

Brachytherapy to the prostate can be delivered in two different ways: permanent seed implants using iodine or palladium seeds and via temporary removable implants using iridium wires. Permanent implants are far more widely used and this review concentrates on this particular form of brachytherapy. The implant procedure itself is imaging-guided but imaging has a major input

into the entire treatment process from patient selection through to evaluation and follow-up after the treatment.

Imaging and patient selection

It is clear from outcome data that proper patient selection is vital to the appropriate use of brachytherapy as a treatment option for localised prostate cancer and imaging has a significant input into the pre-treatment evaluation process. The indications for prostate brachytherapy are very similar to those for any form of radical treatment for prostate cancer; it is a treatment for organ-confined, early stage disease. The imaging work-up is to help identify those patients who are most likely to benefit from brachytherapy — those who are likely to have a good outcome in terms of disease control and associated treatment-related morbidity. Radiologists need to be familiar with certain specific requirements in the assessment of the patient for prostate brachytherapy.

The transperineal approach to the prostate is under the pubic arch and therefore prostate gland volume can have a significant influence on the technical feasibility of this procedure because of so-called "pubic arch interference". Access to the lateral aspects of the gland becomes more difficult as the prostate enlarges and is shielded by the pubic bone. Narrow pubic arches compound the problem and make it difficult to achieve adequate source placement in the lateral and anterior parts of the prostate. This is most likely to occur in patients with gland volumes generally more than 50 cm^3 and in practice this has become the cut-off level for consideration of brachytherapy. Accurate estimation of the prostate volume, not of particular relevance to the surgeon, is therefore essential and correlation with the true gland volume is best achieved with biplanar ultrasound. The radiologist may also need to assess the shape of the pubic arch as part of the initial ultrasound evaluation of the patient[2]. Men with larger volume glands are also more likely to have adverse urinary morbidity after implant and a short course of androgen deprivation therapy (3 months) may be needed to achieve volume reduction prior to brachytherapy and permit technical access to the entire gland in the dorsal lithotomy treatment position.

Patients who have had a transurethral prostate resection (TURP) have a higher risk of incontinence after brachytherapy[3] because of microvascular damage to the urethral blood supply and increased radiation dose to the central part of the prostate. Transrectal ultrasound can be used to measure the residual central gland volume in order to inform the treatment decision process. Whilst peripheral source placement can reduce the dose to the urethra itself, a large cavity may preclude adequate numerical as well as positional source placement in the prostate and it might not be possible to achieve the requisite dose to the whole gland with brachytherapy. The urethra is assumed to be a midline structure for the purpose of radiotherapy planning: an asymmetric urethra, as can occur with benign prostatic hyperplasia or regrowth of central gland tissue into a TURP cavity, can distort the urethra and may even preclude a safe prostate implant. The course and shape of the urethra are important details that the radiologist needs to record and communicate to the medical physicists who are planning the radiotherapy in order to avoid inadvertent trauma to this structure.

Magnetic resonance imaging is used to stage patients prior to brachytherapy to confirm organ confined disease. Detailed evaluation of the prostate margins and seminal vesicles is needed as T3 disease is a contra-indication to brachytherapy as monotherapy. Patients should have no imaging evidence of nodal involvement and currently, only nodal size is used as the exclusion criteria for nodal disease but the role of superparamagnetic iron oxide (SPIO) imaging agents for evaluating the lymph nodes remains to be determined. Staging lymphadenectomy is not part of the work-up for prostate brachytherapy and it should be remembered that the pelvic lymph nodes are not irradiated using this technique.

Current radiation practice is to treat the entire prostate gland, whatever technique (external beam or brachytherapy) is used. The radiotherapy requirements of imaging, consequently, have been to locate and delineate the whole of the prostate gland. Local treatment failure after radiation treatment for prostate cancer is usually intraprostatic at the site of the original primary tumour[4]. It has been demonstrated that local control increases with higher dose[5] and it is therefore reasonable to increase the dose to the site of the primary tumour within the prostate gland. This concept of tumour subvolumes, within the prostate, has generated a need for imaging to target these areas of dominant tumour activity within the prostate. Conventional morphological imaging such as magnetic resonance imaging (MRI) has limitations in depicting such intraprostatic tumour location and activity. Physiological and metabolic-based imaging has therefore been investigated in prostate cancer with the intention of more accurately localising areas of cancer foci within the gland based on altered biology rather than just altered anatomy.

Magnetic resonance spectroscopy (MRS) yields metabolic information about the prostate gland and proton MRS can be used to measure the relative concentrations of citrate, choline and creatine in the prostate. Proton MR spectra of prostate tumours typically show reduced or depleted citrate level and an increased choline level compared with the levels of these metabolites in normal or benign prostatic tissue. MRS can provide a biological profile of the prostate in order to target areas of tumour activity within the gland and might be used to define subvolumes within the prostate for selective boosting with higher implant radiation doses[6] during the implantation. The magnitudes of the spectral changes

appear to correlate with Gleason grade and tumour aggressiveness.

Other physiological imaging techniques might also be of benefit to prostate brachytherapy for localising subvolumes of tumour within the prostate. Dynamic contrast enhanced MRI exploits the neovascularisation seen in cancer tissue to help identify areas of tumour within the prostate. Prostate cancer has demonstrated enhancement patterns that are different from those of benign prostate tissue[7].

Diffusion-weighted MRI enables non-invasive characterization of tissues on the basis of their water diffusion properties. Studies have shown that regions that appear of high signal on diffusion MRI images are associated with more viable tumour tissue, because water molecule diffusion is more restricted by intact cellular membranes[8]. The potential for using this MRI technique to help target viable tumour within the prostate gland lends itself to using it for planning brachytherapy prostate boosts with higher radiation doses.

One of the most important factors for complete control of tumours by radiation is the presence of hypoxic cells within the tumour. Solid tumours often contain areas of hypoxia which are about three times more resistant to radiotherapy than normally oxygenated cells. Such hypoxic tumour foci might therefore require boosting with higher radiation doses in order to maximise tumour control. Blood oxygen level dependent (BOLD) magnetic resonance imaging is an MRI technique that is sensitive to the paramagnetic effects of deoxygenated haemoglobin. It can be used to indirectly measure tissue oxygenation with high spatial resolution. It is another potential imaging technique under evaluation in prostate cancer and it may yield additional information about the spatial localisation of hypoxic prostate cancer areas that may benefit from selective high dose boosts during implantation[9].

Prostate brachytherapy techniques will continue to improve and selective boosting of tumour subvolumes within the prostate gland is both technically possible and radiobiologically desirable. Radiologists involved in this field will therefore need to become familiar with these newer imaging techniques.

Brachytherapy planning

There are different techniques and dosimetry strategies for the actual radiotherapy treatment planning process. The prostate can be scanned some days before the implant, known as pre-planning, or the planning can be performed interactively in the operating room during the implant itself. Whatever approach is used, the procedure for the transrectal ultrasound are similar: the prostate is scanned to obtain an accurate volume and shape and this information is entered into the radiation planning computer in order to generate a three-dimensional dose plan for each particular patient. The transrectal ultrasound data is the basis for calculating the required number and location of sources for that particular patient.

The radiologists needs to be familiar with the concepts of tumour treatment volumes in radiotherapy and needs to liaise closely with the radiotherapist in order to help define the volume to be treated. With prostate brachytherapy, the entire prostate is treated to a minimum peripheral dose of 145 Gy. This is in contrast to an externally administered radiation dose, typically 60—70 Gy. The range of this radiation dose, however, results in an overall prostate dose that extends no more than 5 mm beyond the margins of the gland and so accurate definition of the outline of the prostate is vital to the technical success of the procedure. The radiologist also needs to be familiar with the particular dose constraints that occur with prostate brachytherapy, i.e. the potential dose to the urethra, rectum and penile bulb. The prostate can either be scanned with sequential axial imaging or with 3D volumetric ultrasound. There are no particular advantages to either although certain radiotherapy planning systems may require one or other to be used for raw data ultrasound input.

Imaging guidance for the prostate implant

The implant itself is performed in the operating room with the patient in the dorsal lithotomy position (Fig. 1). General anaesthesia is usually used although occasionally, spinal anaesthesia is utilised. The bladder is catheterized and radiographic contrast introduced into the bladder to facilitate fluoroscopy of the bladder base. This allows safe placement of sources at the prostate base and avoids inadvertent bladder puncture. Fluoroscopy requirements are minimal; with experience the total fluoroscopic time averages 1—2 min per case. Transrectal ultrasound is used to image the prostate in both axial and sagittal planes and a template is placed on the perineum to facilitate needle insertion into the prostate. The role of the radiologist is to monitor needle insertion and source deposition in the prostate as the implantation procedure progresses.

Iodine-125 is most commonly used although some centres use palladium sources. There is no evidence that either isotope has any clinical advantage over the other. Iodine-125 has a half-life of 59.4 days and it emits gamma-rays with maximum energy of 35 keV. This low energy is associated with a tissue range of approximately 3—4 mm. Each of these sources, or "seeds", is made of titanium, 5 mm in length and 1 mm diameter. These sources are preloaded into 18-gauge needles and usually, 2—3 sources per cm^3 of prostate tissue are required to achieve the requisite dose of 145 Gy to the whole gland. On average 25—30 needles are used for each procedure and each needle can contain up to seven sources.
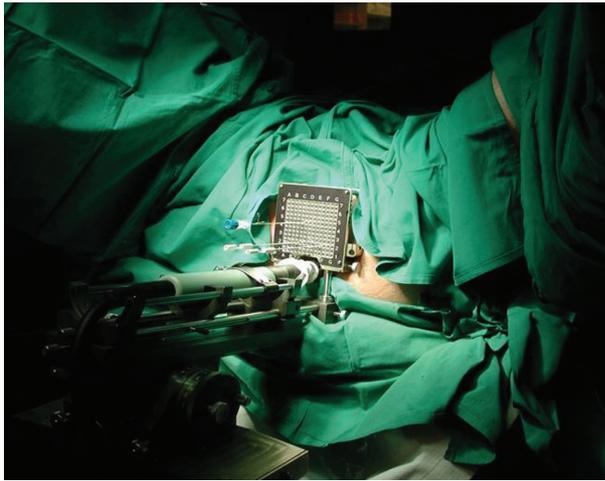
Figure 1 **Template-guided transperineal technique with patient in dorsal lithotomy position.**
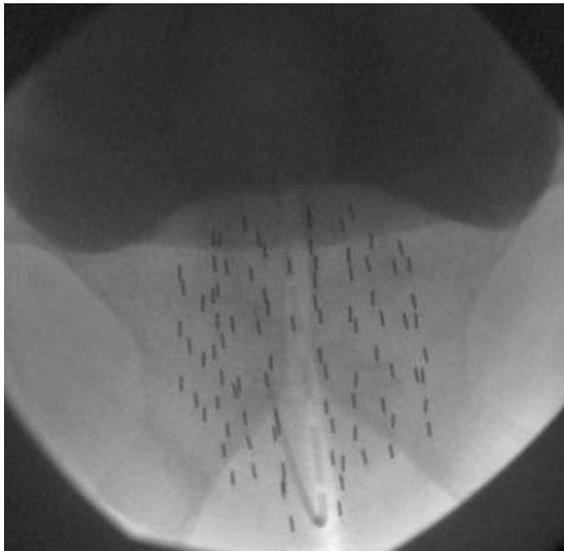
Figure 2 **Post implant radiograph.**

Biplane ultrasound allows each needle to be monitored as it is inserted transperineally into the prostate. Great care must be taken to avoid inadvertent trauma to the bladder, urethra and rectum during insertion. Care must also be taken to avoid needle insertion into the bladder. When the radiologist is satisfied that each needle location is correct, the seeds can then be unloaded into the prostate by withdrawing the needle over the stylet. Seed position in the prostate can then be confirmed on ultrasound and fluoroscopy (Fig. 2). The entire implant procedure takes about 45 min on average with most patients are discharged home within 24 h. Prostate brachytherapy using this seed implant technique is a one-off procedure. The sources are retained permanently in position after the implant and their position cannot be altered. No further radiation to the prostate is usually possible and hence the critical need for accurate prostate localisation and seed placement from the outset.

Imaging for follow-up

It should be remembered that there is an ever-increasing number of men who have had prostate implants in the community and radiologists should be familiar with the appearances on plain radiographs as well as on cross-sectional imaging as these patients may subsequently have imaging for some other condition.

The prostate can be re-scanned immediately after the implant with transrectal ultrasound to assess source placement[10] but it is very difficult to consistently identify all sources within the prostate. Fresh haemorrhage and oedema often obscure good source visualisation and ultrasound-based post implant dosimetry cannot be used for consistent reproducible measurements.

Follow-up after brachytherapy is clinical and imaging has a limited role for direct patient management. Standard practice has been to perform a computed tomography (CT) scan some 4–6 weeks post implant by which time any prostate oedema has usually settled. It should be appreciated, however, that these scans cannot alter an individual patient's management: brachytherapy is a one-off treatment that cannot be repeated or subsequently modified. The contribution of post-brachytherapy CT scanning is to assess implantation quality and predict the likely outcome and complications. Post implant CT based dosimetry provides qualitative information that can be used to monitor individual brachytherapy programmes and allows comparison between institutions. The quantitative evaluation of implant quality using CT-based dosimetry provides feedback to the implant team and also forms a basis for evaluating development of the technique. Although the seeds are easily identified on CT scanning, the prostate is notoriously difficult to outline accurately, especially at the base and apex of the gland. Small contour changes can have a major impact on observed dosimetry and it has been consistently shown that CT overestimates the volume of the prostate as referenced to ultrasound or MRI scanning[11,12]. Radiologists may contribute to this post-implant assessment by contouring the prostate on CT scans and marking sources on sequential images of the gland. This data is then used by the medical physicists to calculate the administered dose to the prostate gland.

MRI has also been used to assess the prostate post implant. In contrast to CT, source visualisation is not as good as with CT but the prostate margins are much more accurately identified. A variety of sequences have been used and there is no one sequence that can be regarded as universally applicable to all scanners. It is, however, expensive and again it cannot alter the management of the individual patient. Fusion studies using CT and MRI

Figure 3   **Fused CT/MRI post implant scans.**

have been performed (Fig. 3) but the benefit is unclear and fusion techniques have yet to find a routine role in clinical brachytherapy practice.

Biochemical control

The development of prostate brachytherapy as an alternative to radical surgery and external beam radiotherapy has generated considerable clinical interest in its value and clinical outcomes. Clinical endpoints for any form of treatment for early prostate cancer are unclear: with its long natural history, overall survival is less relevant for prostate cancer than for other cancers with a much shorter biological timescale. Biochemical control is widely used and yet the prognostic value of prostate-specific antigen (PSA)-free progression is debatable in terms of patient outcomes. As radiologists, we have become familiar with evaluating the contribution of imaging in terms of its diagnostic impact and therapeutic ratio[13] but imaging-guided prostate brachytherapy remains difficult to evaluate in these terms. The value of imaging will have to be extrapolated from the long-term impact on patient survival and quality of life.

Prostate brachytherapy data has now matured as a treatment with consistent results reported from the major centres in the US and Europe. For good prognosis patients (PSA <10 ng/ml, Gleason score <7) brachytherapy alone produces excellent rates of biochemical control with reported rates of 87–96% with 10-year follow-up[14–18].

The impact of adverse prognostic factors such as presenting serum PSA and Gleason score on biopsy is consistently demonstrated in these series. Intermediate risk patients (PSA 10–20 ng/ml, Gleason 7) have biochemical control rates slightly lower than for the good prognosis group[18,19]. Brachman[20] reported a

5-year biochemical control rate of 53% for high risk patients (PSA >20 ng/ml, Gleason >7) and D'Amico's series[21] reported only 35% PSA-free disease at 5 years. These higher risk patients may not be ideal candidates for brachytherapy as monotherapy and alternative treatment techniques such as high dose rate brachytherapy with temporary iridium implantation or a combination of brachytherapy and external beam radiation may eventually yield better results for this group of men. The value of giving additional hormonal therapy to patients with intermediate and high risk cancers is questionable and no consistent data has yet emerged for brachytherapy in combination with hormonal manipulation. The Leeds data[22] failed to show a benefit from the addition of such adjuvant hormonal manipulation.

After successful radiation treatment for prostate cancer, patients will show a decrease in their serum PSA levels. There is, however, a phenomenon of a temporary increase in the serum PSA followed by a further decline. This has become known as the "PSA bounce"[23] and radiologists involved with the management of these patients need to be familiar with the phenomenon to avoid over-zealous prostate biopsy and perhaps inappropriate salvage therapy following prostate brachytherapy. Definitions of this PSA bounce vary but it is generally seen in about 30–60% of all patients treated with brachytherapy. It usually occurs 12–24 months following implantation and on average persists for about 12 months. It has been proposed that PSA bounces are probably the result of some mechanism compromising membrane integrity (i.e. radiation-induced prostatitis) in PSA-producing epithelium.[24,25] The magnitude of the bounce is rarely >1.0 ng/ml and there does not appear to be any clinical significance in terms of ultimate disease control. Prostate biopsies can be misleading in this situation as prostate histology may take up to 3 years to show complete eradication of tumour after brachytherapy.

Imaging for suspected relapse

The biochemical definition of failure following radiotherapy has varied in the literature[26] but whatever definition is used, the question of imaging to locate the site(s) of tumour recurrence may arise. Conventional MRI of the irradiated prostate is of little value and confirmation of local recurrence will have to depend on prostate biopsy in most cases. There may be a role for MRS in this clinical situation as increased metabolic activity within the implanted prostate may indicate local recurrence but this is still an area of research. In practice, exclusion of metastatic relapse with CT scanning and bone scanning will be used as indirect evidence of local failure. The indications for imaging in patients with biochemical failure, however, must be carefully considered in clinical context. Salvage treatment options are limited and in most cases not likely to be influenced by the imaging findings.

Figure 4 **Inadvertent seed placement into right side of penile bulb.**

Morbidity after prostate brachytherapy

Most patients will experience some urinary symptoms after prostate brachytherapy and acute urinary retention generally occurs in about 15–20% of patients[27–30]. Nocturia and daytime frequency are very common and overall urinary morbidity does correlate with higher pre-treatment urinary International Prostate Symptom Score (IPSS). The relationship of urethral dose to urinary toxicity is unclear although most patients benefit from routine prophylactic use of alpha blockers (smooth muscle relaxants) during the initial weeks after implantation[31]. Prolonged urinary catheterisation is unusual and surgery to improve urinary flow should be avoided if at all possible as it has a high risk of causing incontinence afterwards. The reported risk of developing a urethral stricture at 5 years varies from 5 to 12%[31,32].

Rectal complications are uncommon and usually consist of self-limited proctitis[33–35]. Rectal bleeding peaks at 8 months after implant with an incidence of 4–11% and usually resolves spontaneously. Long-term bowel dysfunction after brachytherapy is very unusual. Fistulas[36] are rare and it is important that deep anterior rectal wall biopsy is avoided in this group of patients.

Preservation of sexual function after brachytherapy[37], in common with other treatments for prostate cancer, is difficult to assess but is probably not as good as originally believed. Erectile dysfunction is this age group is invariably multifactorial in origin. The only series using a validated quality of life scoring system reported 52% maintenance of erectile function at 6 years after prostate brachytherapy as monotherapy[38]. Radiation dose to the penile bulb is likely to prove significant in this regard and future efforts may require specific dose restriction to the penile bulb at the time of radiotherapy planning. Radiologists may be required to carefully delineate the penile bulb on ultrasound in order that the planned dose can be reduced[39]. Care must also be taken during the implantation procedure to avoid misplacement of radioactive seeds into the penile bulb (Fig. 4).

Future developments

The techniques of prostate brachytherapy continue to evolve and the major impetus now is to develop interactive techniques that rely on real-time feedback dosimetry about source placement to update and modify subsequent needle placement during the implant itself. This will reply heavily on radiological input during implantation if implant quality is to be improved using these newer techniques. Patient selection will improve as data continues to mature. Radiation planning systems will develop and better ultrasound will aid seed visualisation both during and after the implant. We have learned that prostate brachytherapy is an effective treatment but there is a learning curve and the quality of the implant matters in terms of outcomes. Quality assurance programmes will assume a major role for a treatment that is a monotherapy and cannot be corrected at a later date.

Conclusion

Prostate brachytherapy has become a widely accepted and valid method for the treatment of localised prostate cancer. Imaging is central to appropriate patient selection, the safe performance of the implantation itself as well as patient follow-up afterwards to provide feedback data on implant dosimetry. Prostate brachytherapy requires close collaboration with medical physicists and radiation oncologists and the contribution of radiology will increase further as the diagnosis of early stage prostate cancer increases and more men opt for this therapy based on favourable survival and quality of life outcome data.

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