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BRACHYTHERAPY DOSIMETRY SPECIAL FEATURE: REVIEW ARTICLE

Recent developments and best practice in brachytherapy treatment planning

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ABSTRACT

Brachytherapy has evolved over many decades, but more recently, there have been significant changes in the way that brachytherapy is used for different treatment sites. This has been due to the development of new, technologically advanced computer planning systems and treatment delivery techniques. Modern, three-dimensional (3D) imaging modalities have been incorporated into treatment planning methods, allowing full 3D dose distributions to be computed. Treatment techniques involving online planning have emerged, allowing dose distributions to be calculated and updated in real time based on the actual clinical situation. In the case of early stage breast cancer treatment, for example, electronic brachytherapy treatment techniques are being used in which the radiation dose is delivered during the same procedure as the surgery. There have also been significant advances in treatment applicator design, which allow the use of modern 3D imaging techniques for planning, and manufacturers have begun to implement new dose calculation algorithms that will correct for applicator shielding and tissue inhomogeneities. This article aims to review the recent developments and best practice in brachytherapy techniques and treatments. It will look at how imaging developments have been incorporated into current brachytherapy treatment and how these developments have played an integral role in the modern brachytherapy era. The planning requirements for different treatment sites are reviewed as well as the future developments of brachytherapy in radiobiology and treatment planning dose calculation.

CHANGES AND DEVELOPMENTS IN TREATMENT PLANNING TECHNIQUES

Within the past few decades, there have been some major changes to the way brachytherapy treatments are both planned and delivered, and the introduction of modern, three dimensional (3D) imaging techniques have contributed significantly. In the 1930s, before the advent of planning computers, treatment planning was carried out by simply following a set of rules according to a dosimetry system such as the Manchester system.^{1–3} This system was originally developed for use with radium sources and provided information, in tabular form, for the dose specification and distribution of sources and was used for many years. An increase in radiation safety awareness in the 1970s and 1980s led to a decline in the use of radium in favour of the relatively newer and safer radioisotopes such as caesium-137 and iridium-192. Over the same period, technological advances in afterloading techniques and the wider implementation of computerized planning using planar radiographic imaging were being implemented in an attempt to verify the applicator or catheter positions and calculate patient-specific dose. Alongside these advances,

the need to compare patients' treatments with those from other treatment centres was being recognized as an important scientific standardization of treatment. The International Commission on Radiation Units and Measurements (ICRU) reports 38 and 58,^{4,5} details the dose and volume specification required for intracavitary therapy in gynaecology and interstitial therapy, respectively.

The use of two-dimensional (2D) imaging remained integral to treatment planning for many years, despite its limitations such as the inability to report any specific dose–volume information for the tumour or organs at risk (OARs). More recently, however, significant technological advances have resulted in the use of newer imaging modalities, planning algorithms and treatment delivery techniques. International working groups have published recommendations detailing new terms and planning parameters to be determined when carrying out full 3D-image-guided treatment and how to use these data in order to standardize the reporting and prescribing of brachytherapy treatments.^{4–9}

Acquiring a 3D data set using CT and/or MRI has enabled more accurate planning and better dose determination to volumes of both the tumour and the OARs. In much the same way that intensity-modulated radiotherapy and modulated arc therapy have advanced the way external beam radiotherapy (EBRT) is planned and delivered, so too have 3D-image-guided and planning techniques advanced the field of brachytherapy.

In addition to the change in imaging and planning techniques, there has also been a change in treatment delivery. The previously well-established low-dose rate (LDR) manual afterloading for interstitial treatments and caesium-137 medium-dose rate (MDR) modality for gynaecological treatments have been superseded in the main by high-dose rate (HDR) and pulsed-dose rate (PDR) remote afterloading. The long treatment times associated with MDR cervix brachytherapy (typically 24 h), the inability to conform the treatment isodose distribution to the area of interest and, probably most importantly, the ceasing in manufacture of the treatment machine and sources have been the main reasons for the shift to HDR. This has inevitably resulted in an increase in the use of HDR as a treatment modality and with it, the advantages of shorter treatment times, the ability to carry out dose optimization from the use of single stepping source technology and also the greater flexibility for this machine to be used for a much wider range of treatment sites. PDR was developed specifically for gynaecological brachytherapy in an attempt to simulate the radiobiological properties of MDR, utilizing the advantages of the same stepping source technology as seen in HDR. In this case, a large number of small fractions (pulses) are delivered in the same overall time taken for the MDR treatment, with one pulse every 1–4 h. It should be noted that LDR treatments are still a recognized standard treatment modality in the field of prostate brachytherapy, where small palladium-103 or iodine-125 seeds are permanently implanted into the organ.

CLINICAL BRACHYTHERAPY PLANNING

The need for efficiency and accuracy

When treating brachytherapy patients, there are several distinct processes: volume delineation of the tumour and OARs, applicator reconstruction, dose calculation and treatment. It is usual that the planning and treatment will occur during the same day and sometimes even within the same theatre session. This is often quite different from the most common EBRT scenario, where it is usual for the plan to have been computed quite sometime before the patient receives his/her treatment. As a result, brachytherapy planning systems with efficient tools for outlining on optimized data sets, accurate applicator reconstruction methods and fast dose computational algorithms are essential to minimize any delay between the initial image acquisition and eventual treatment.

Defining accurately where to target the radiation and also where to avoid delivering dose is essential in brachytherapy owing to the very steep dose gradients involved and will depend on the body site to be treated. In modern brachytherapy, the imaging modality used is typically CT, MR or ultrasound, which enables the target and OARs to be outlined and, in addition, the computation of dose–volume histograms (DVHs). The true value of these DVHs is therefore dependent on the accuracy of the corresponding target/organ delineation. There is a clear need for delineation

protocols such as the recommendations from the European Gynaecological Groupe European de Curietherapie-European Society for Radiotherapy and Oncology (GEC-ESTRO) GYN working group^{6,7} and the American Brachytherapy Society (ABS) guidelines,^{8,9} as it is important to achieve consistent treatments so that results can be reliably compared between different centres. There have been several studies carried out studying the effect of the dosimetric impact of interobserver variability when delineating structures. One such study by Hellebust et al¹⁰ looked at this effect for cervix brachytherapy and compared six patients outlined by ten observers worldwide. Both the target D_{90} (the minimum dose received by 90% of the target) and the OARs D_{2cc} (the lowest dose received by the most irradiated 2 cc) were analysed. The interobserver delineation variation (IODV) in the high-risk clinical target volume (HRCTV) caused an uncertainty in the D_{90} of ± 5 Gy [1 standard deviation (SD)] and in the OAR D_{2cc} by ± 2 –3 Gy (1 SD). (The doses are in terms of 2 Gy equivalent, EQD2, using $\alpha/\beta = 10$ for the HRCTV and $\alpha/\beta = 3$ for the OAR.) The dosimetric impact was smallest for the gross target volume (GTV) and HRCTV, whereas the IODV had smaller impact on the bladder and rectum. In another study by Dimopoulos et al,¹¹ 19 cervix patients' HRCTVs were outlined by two observers following the GEC-ESTRO GYN recommendations. The D_{90} and D_{100} were assessed. The maximum volumes of the GTV and HRCTV did not differ significantly ($p > 0.05$). Significant differences were noted, however, for the intermediate-risk clinical target volume (CTV) ($p < 0.05$). They concluded that the application of recommendations for image-guided brachytherapy (IGBT) contouring produces acceptable interobserver variability and that the differences found were owing to image contrast and neglecting to consider anatomical borders. A further study by Saarnak et al¹² showed that by taking the interobserver variation caused by delineation differences into account, doses in the bladder and rectum could be determined within an accuracy of about 10% (1 SD).

Another aspect of the planning process that influences the treatment accuracy is the ability to place the applicator optimally in the treatment area. In the case of cervix brachytherapy, the applicator can be more reliably positioned with the aid of trans-abdominal ultrasound guidance as reported by Davidson et al.¹³ They reported that 34 from 35 insertions were successfully completed with no uterine perforation. Furthermore, improvements in online imaging techniques using ultrasound guidance for HDR prostate treatments, for example, have enabled the treatment catheters to be accurately positioned and reconstructed compared with using CT imaging.¹⁴

Most treatment planning is carried out with the aid of 3D imaging modalities, such as CT and MR, after the applicators have been inserted. MRI has the advantage of being able to define soft tissue and so can distinguish between tumour and normal tissue, but often a combination of CT and MR is used. Most modern planning systems have a library of virtual applicators, which can be manipulated within the software such that the virtual and real applicators are exactly superimposed. With the applicators reconstructed and outlines delineated, a 3D plan can then be computed.

The final part of the planning process is the dose calculation. Most modern brachytherapy planning systems use the American

Association of Physicists in Medicine (AAPM) recommendations laid out in the TG43 and TG43 U1 formalism (Nath et al¹⁵ and Rivard et al¹⁶). This formalism is based on measured or measurable quantities either by thermoluminescent dosimeter (TLD) or Monte Carlo (MC) methods, produced by a source in a uniform water-equivalent medium. This recommended dosimetry protocol provides a clear definition of the physical quantities, and the equations required to calculate dose from a single source.

It is currently unusual for commercial brachytherapy planning systems to use MC modelling or to consider the inhomogeneities of real life situations, such as applicator shielding, interseed attenuation (in the case of prostate seed treatment), tissue attenuation and air cavities etc. In 2009, Rivard et al¹⁷ summarized the effect of such omissions and the uncertainties associated with the TG43 algorithm. He concluded that the effect would be greater for low-energy photon emitters, such as iodine-125 compared with iridium-192. Nevertheless, the absorbed dose to water compared with tissue for low-energy emitters is -4% compared with +2% for high-energy emitters. In order to reduce the dosimetric uncertainties and improve the accuracy of the calculation, especially for low-energy emitters, further work has to be carried out examining the effect of brachytherapy source photon interactions in a real life heterogeneous, bounded medium.

There are, as discussed, many sources of uncertainty in the planning process, including organ and tumour delineation, applicator placement and reconstruction, source strength calibration and dose calculation. The need for accurate planning requires all of these areas to be considered and implemented accurately within the planning process with careful attention to detail. A recent, extensive review of clinical brachytherapy uncertainties has been published, giving guidelines on behalf of ESTRO and the AAPM.¹⁸ The excellent article examines the uncertainties associated with source strength, treatment planning, medium heterogeneity, imaging and source position and temporal accuracy. It considers the effect at the patient level giving examples in vaginal and cervix brachytherapy, breast balloon brachytherapy and both LDR and HDR prostate brachytherapy, finally providing specific recommendations for uncertainty reporting.

The treatment planning process is becoming quite complex with the introduction of 3D IGBT, implant/insertion procedures requiring a general anaesthetic and a team of dedicated staff consisting of clinicians, physicists, radiographers and nursing staff. There has to be a limit to the degree of complexity in order to achieve a clinically acceptable plan. The time spent outlining the OARs, for example, has to be offset against the organ movement occurring between outlining and treatment. Moreover, for cervix brachytherapy, since imaging and planning is carried out after the applicator insertion procedure, any delay in this process could be detrimental for patient treatment. The planning process, therefore, should be optimized to reduce any unnecessary delay. Any changes to the planning system software introduced by the manufacturer, such as new applicator reconstruction methods or dose calculation algorithms, which may include MC modelling methods, should not introduce any significant increase in time to the overall procedure.

IMAGING DEVELOPMENTS IN TREATMENT PLANNING

Early brachytherapy procedures involved mainly 2D imaging using orthogonal radiographs where the applicators were reconstructed and a dose distribution relative to this reconstruction was calculated.¹⁹ Using this technique, it was difficult to calculate and impossible to know the dose to the tumour exactly, as soft-tissue visualization is poor using tube potential radiography. Modern 3D imaging techniques have recently formed an integral part of the planning process for many treatment sites, made possible by the increasing availability of high-quality imaging equipment. Prostate implant treatments have benefited from the ready access of standard ultrasound imaging equipment allowing CTV localization and dose limiting structures to be identified via transrectal ultrasound-guided (TRUS) procedures.^{20,21}

CT and/or MRI, in particular, is now recommended in the UK for planning cervix brachytherapy cases with guidance for volume definition, DVH parameters and dose prescription.²²

With the use of this imaging, new concepts have emerged based on the availability of volumetric data. Parameters in cervix brachytherapy, such as the HRCTV, D_{90} and D_2 cc for the OARs, have been described⁶ and allow a robust set of planning parameters leading to better consistency. The superior capability of MR compared with CT in visualizing soft tissue has resulted in MR becoming a crucial part of the imaging process, which is most notable in tumour definition. A study by Viswanathan et al²³ showed that the use of CT to outline the tumour could overestimate the volume leading to unnecessary higher doses to the OARs. There is a growing body of evidence showing that MR is far superior to CT for delineating the tumour volume at the time of brachytherapy^{6,24,25} and, in much the same way as the concept of point A became the standard for prescribing the dose in 2D cervix planning, the HRCTV will become the standard structure to use for the dose prescription using 3D IGBT. This will lead to a more routine approach to planning and the ability to carry out new clinical studies with systematic evaluation of clinical outcomes.

Furthermore, as already stated, different imaging modalities provide different information for treatment planning and the requirement to combine image data sets within the same plan has resulted in the development of image registration and fusion techniques. These modalities image the same tissues differently and the fusion techniques provide sophisticated tools to help differentiate between the tumour and the normal tissue and inform the decision-making process. However, the ultimate decision of what to treat and what not to treat still remains with the clinician. A publication by Kessler²⁶ provides an overview of the techniques used in radiotherapy with examples of their use.

Alongside these state-of-the-art imaging modalities and fusion techniques comes the need for manufacturers to provide new treatment applicators compatible with the particular modality to ensure good quality visualization for the purposes of treatment planning. Non-ferro-magnetic applicators for use with MR and CT have been developed, and there are now many suitable applicators available in the market place for a variety of treatment sites.

PLANNING REQUIREMENTS FOR DIFFERENT TREATMENT SITES

There are many clinical sites able to be treated with brachytherapy, including regions of the head and neck, bronchus, oesophagus, breast, prostate, many gynaecological sites, rectum, anus and surface lesions. The following sections will describe some of the treatment sites that have witnessed major advances over the past 10–20 years following the introduction of more sophisticated planning and treatment techniques, applicator design and imaging modalities.

Breast

Brachytherapy has been used for many years as a technique to deliver a boost dose to the surgical site following a course of whole breast irradiation, as part of breast conserving therapy; although, in this setting, external beam electron or photon boosts are more common. That said, brachytherapy techniques result in excellent local control rates,^{27–29} and when applied correctly, the cosmetic results are comparable to those achieved with external irradiation boosts.³⁰ A technique for treating the breast that has developed over recent years is partial breast irradiation.

Accelerated partial breast irradiation

Breast conserving surgery followed by radiotherapy is still considered to be the standard of care for many early stage breast cancer cases and, which has been demonstrated in a number of clinical trials, is equivalent in terms of survival to mastectomy.^{31–33} The need for adjuvant radiotherapy is a critical part of the treatment for tumour control, which if omitted could significantly increase the ipsilateral failure rates.^{34,35} Further studies have shown that the majority of these ipsilateral breast failures in patients not receiving adjuvant whole breast radiotherapy occurred within the tumour bed.^{36,37} Additional data from van Limbergen et al,³⁸ Clark et al³⁹ and Vaidya et al⁴⁰ demonstrated that at least 90% of failures occur within the index quadrant. As a consequence of these and many other similar studies, the concept of partial breast irradiation has developed as a method of delivering the radiation part of the treatment by targeting the tumour bed alone, with a suitable margin, as opposed to the whole breast. The accelerated term in accelerated partial breast irradiation (APBI) means that the radiation can be delivered within 1 week, offering patients the convenience of and reducing the complexities of coordinating 4–6 weeks of daily treatment.

APBI can be easily delivered using brachytherapy techniques. The principal advantage of using brachytherapy is the inherent rapid fall-off of doses away from the radiation source, reducing the irradiation of any surrounding normal tissue, such as lungs, ribs, heart (for left-sided breast) and skin. Also, while the requirement to expand the treatment volume to allow for patient movement and setup errors is an essential part of EBRT techniques, it is not necessary with brachytherapy, and as such, smaller irradiated volumes are possible. There are several conflicting publications detailing the late toxicity effects of irradiating larger volumes of tissue;^{41–45} nevertheless, smaller irradiated volumes achieved with brachytherapy may reduce the risk of late toxicity.

With the concept of APBI growing in popularity, the GEC-ESTRO group and the ABS have published recommendations

for patient selection,^{46,47} and two important international trials have been set up to establish the efficacy of APBI.^{48,49} These include dosimetric requirements for treatment planning in terms of doses to the planning target volume (PTV) and the normal tissue.

Several innovative brachytherapy treatment delivery methods have emerged for APBI and have been reviewed by Njeh et al.⁵⁰

Interstitial multicatheter implants

This treatment technique was the first to emerge as a successful method of delivering APBI and, as such, has the most mature follow-up data.^{51–54} The technique involves implanting a series of catheters in and around the tumour bed using a template to guide the catheters.⁵⁵ The use of a template to position the catheters is essential to achieve accurate dosimetry. The catheters are implanted with an intercatheter spacing of, typically, 10–15 mm in a number of parallel planes depending on the volume to be treated. The catheter cross-section is either in the form of squares or equilateral triangles following the Paris implant dosimetry system,⁵⁶ which is also used to determine the number and separation of the catheters. The use of rigid needles obviates the need for CT planning since ideal geometry can be achieved. However, for fractionated APBI with 7–10 fractions over 4–5 days, plastic catheters are more common for a patient's comfort. These are also inserted via a template system, which is then removed leaving the catheters *in situ*. Since the geometry is not rigid, the best practice is to use full 3D CT planning to achieve good dosimetry. The ESTRO trial protocol⁴⁸ requires that 100% of the prescribed dose covers at least 90% of the PTV and that the maximum skin dose should be <70% of the prescribed dose, whereas the National Surgical Adjuvant Breast And Bowel Project (NSABP) trial⁴⁹ requires that at least 90% of the PTV should receive at least 90% of the prescribed dose. In addition, care must be taken to avoid treating large contiguous volumes to high doses. The V_{150} (the volume of the breast tissue receiving 150% of the prescribed dose) should be minimized, as it has been associated with an increased risk of late toxicity if it is >45 cc,^{57,58} although the NSABP trial requirement is for the V_{150} to be <70 cc.⁴⁹

Intracavitary balloons

In an attempt to re-energize the use of brachytherapy for breast treatments owing to the inherent technical complexity of the interstitial technique, the concept of balloon brachytherapy emerged in the early to mid 2000s with the development of the MammoSite® (Hologic Inc., Marlborough, MA) applicator. This device consists of a silicone balloon with two channels—a central channel allowing remote afterloading of an HDR source and a second channel for balloon inflation to a diameter of 4–5 cm, once inserted in the lumpectomy cavity. The placement of the balloon can either be at the time of surgery or during a post-operative procedure in an outpatient setting. Treatment planning is carried out from CT data where suitability for treatment is checked (Figure 1). Firstly, the distance of the inflated balloon surface from that the skin is assessed—a distance <15 mm has been shown to increase the risk of skin toxicity,⁵⁹ and secondly, the conformance of the balloon to the cavity is checked, as surrounding air spaces or haematoma will be detrimental to the

dose distribution since a dose of typically 34 Gy in ten fractions over 1 week is prescribed at 10 mm from the balloon surface in a plane transverse to the MammoSite catheter at the balloon centre. The PTV is a shell formed by subtracting the cavity from a volume created by expanding the cavity volume by 1 cm in 3D, with the skin and chest wall contours removed. The NSABP trial⁴⁹ requires that at least 90% of the PTV should receive at least 90% of the prescribed dose. A publication from Vargo et al⁶⁰ from a single institution, which retrospectively reviewed 157 patients who had undergone APBI with MammoSite, showed good tumour control and breast cosmesis at 5 years with minimal late toxicity, although it was noted that skin toxicity was a function of the skin dose. To address the inability of optimizing the dose distribution with the MammoSite single lumen system, new multilumen balloon devices are now available, which combine the implant simplicity of the MammoSite with the complex dosimetry potential afforded by the multi-channel interstitial technique. Treatment planning for these multilumen devices involves optimizing the prescription dose of 34 Gy to a PTV created as described earlier. The extra channels in the applicator allow for better dose optimization by being able to sculpt the dose away from the skin or underlying chest wall, while still being able to achieve at least 95% of the prescribed dose to 95% of the volume.^{61–63} In addition, for balloon breast brachytherapy, the V_{150} should be kept low and is required by the NSABP trial protocol to be <50 cc.⁴⁹

Electronic breast brachytherapy

The term electronic brachytherapy combines the concept of brachytherapy, that is, short distance therapy usually associated

with radioactive sources but with electrically generated, low-energy, 50-kV X-rays. Several devices have recently appeared on the market and the commissioning process of one such device used for electronic breast brachytherapy has been described by Hiatt et al⁶⁴ and shows that the depth-dose characteristics are similar to low-energy photons with a dose distribution roughly spherical with rapid fall-off. In this device, a miniature, water-cooled photon source is driven by the system into a balloon, which was previously placed in the cavity created either at the time of surgery or post-operatively. The device is then turned on at appropriate positions within the balloon for pre-programmed dwell times to deliver the prescribed dose. The administration of the radiation using this device can be delivered more conveniently without the need for any special shielding, thereby reducing the cost. Since the X-rays generated are of low energy with a tenth value layer in lead of about 1.6 mm, a small mobile shield can be used in the treatment room to reduce the dose to the operator and, in addition, shielding local to the treatment site can be applied. Recommendations for electronic brachytherapy have been published by the AAPM in report 152.⁶⁵ A dose of 34 Gy in ten fractions is prescribed at 10 mm from the balloon surface. This treatment method is, however, associated with an increased volume of breast tissue in the high-dose regions and a decreased dose to the adjacent normal tissues compared with MammoSite HDR APBI treatments.⁶⁶ It should be noted that this electronic brachytherapy treatment technique is still, however, very much in its infancy and more clinical data are required before any reliable conclusions can be drawn regarding its equivalence to standard treatments.

Gynaecology

Whilst brachytherapy is recognized as a valuable treatment modality for a variety of gynaecological sites, such as vulva, vagina and endometrium, it is the treatment and planning of carcinoma of the cervix that has seen the greatest development in recent years.

Cervix (simple two-dimensional vs three-dimensional treatment planning)

The most common treatment site where brachytherapy has been shown to play an integral part in the radiotherapeutic management, is that of the cervix.^{67,68} Traditional methods for this treatment were first developed in the 1930s around the use of radium and the Manchester dosimetry system.¹ Intrauterine and vaginal sources were inserted according to specific standard loadings to deliver almost constant LDR to a reference point, and, in principle, assuming perfect geometry, the treatment could be delivered with rudimentary radiographic imaging and no computer planning. MDR caesium-137 was used extensively from the 1960s initially via a manual afterloading technique where source trains of caesium-137 were manually afterloaded into applicators, which had been positioned in the patient during a minor operative procedure. This manual loading technique started to be replaced in the late 1970s with the introduction of automated pneumatic systems, such as the Selectron unit, which contained small, 2.5-mm diameter caesium-137 pellets that could be arranged with inactive spacer pellets, into source trains of 48 per train.⁶⁹ Each train could then be driven remotely, via compressed air into the appropriate

Figure 1. Axial CT section showing the dosimetry for accelerated partial breast irradiation using a balloon catheter.

patient applicator. The applicators consisted of an intrauterine tube or tandem and two ovoid tubes. Treatment planning was fairly simple and was carried out using a pair of orthogonal radiographs: an anteroposterior and a right or left lateral. By inserting radio-opaque markers into the applicators, they could be visualized from standard radiographic imaging and then reconstructed in the planning system via a digitization method. The dose was prescribed to the internationally established prescription point A, which is described in the Manchester system.¹ Point doses to be calculated for the rectum and bladder were recommended by the ICRU.⁴ This 2D treatment planning via an orthogonal pair of radiographs remained the standard method for cervix brachytherapy until the late 1990s with many technical improvements throughout this period. Dedicated brachytherapy imaging equipment was developed, which enabled the planar images to be transferred directly to the planning system and improvements in applicator reconstruction techniques were being included in the planning system by the manufacturers. However, despite these improvements, the basis of treatment planning still remained 2D with no tumour or organ volume information. With the widespread acceptance of CT and MRI in EBRT, a study published in 2007 by a group in Vienna, investigated the clinical impact of MRI-based cervix brachytherapy combined with external beam chemoradiation.⁷⁰ In this study, dose-volume adaptation and dose escalation was applied in a consecutive group of patients with locally advanced disease. They compared patients planned using the simple 2D technique to those who had been planned using more complex 3D volume-based planning utilizing MRI. The results showed that with 3D MRI-based planning, local control of $\geq 85\%$ could be achieved with low treatment-related morbidity: Grade 3/4 of 6% compared with 13% using simple 2D planning methods. They suggested that for locally advanced limited disease, the MRI-based approach will likely result in assuring excellent local control ($\geq 95\%$) and minimize treatment-related morbidity. The need to implement 3D imaging for cervix brachytherapy has since been recognized by European, US and UK groups, such as ESTRO, and the Royal College of Radiologists (RCR) who have published recommendations detailing the requirements for 3D cervix planning.^{6,9,22} With improvements in treatment planning systems, applicator design sympathetic to the imaging modality and the ability to visualize tumours and OARs, image data can be transferred to planning systems where volumes of tissue can be outlined and DVHs calculated and reported. Manufacturers have introduced virtual applicator library models in the planning systems, which, when implemented correctly using critically designed quality assurance programmes, improve the speed and accuracy of the applicator reconstruction. The clear benefit of 3D planning in this setting is that there is a potential to optimize the dose to the outlined tumour volume, while maintaining acceptable doses to the OARs, thereby reducing the long-term toxicity (Figure 2). There have been many publications illustrating this effect.^{71–75} In addition, the traditional point A dose has been shown to be a poor surrogate of the HRCTV dose and that MRI-based IGBT significantly improves target coverage and OAR dose.⁷⁶

It is important that with the change from 2D to 3D treatment planning, the need to follow the recommended published

guidelines is paramount to allow consistency of treatment and reliable data comparisons to improve the overall treatment results.

Prostate

The prostate gland is arguably an ideal site for brachytherapy and many implant methods have been developed in the early part of the last century.⁷⁷ It was during the 1980s, however, that prostate brachytherapy took a major step forward as a result of the combined effect of new imaging modalities, 3D planning systems and manufacturers developing more convenient forms of radioisotopes.

Low-dose rate seed implants

The standard method for implanting radioactive iodine-125 seeds into the prostate is via the perineum. The prescribed dose as recommended by ESTRO and the ABS is 145 Gy to the whole prostate with a 2- to 3-mm margin.^{78–80} This technique has been described and popularized in several publications.^{81–84} Needles are inserted through a grid system, which provides the x (left/right) and y (anterior/posterior) coordinates. The grid is mounted on a stepper unit holding a TRUS transducer allowing the depth, z (superior/inferior) information to be acquired. The origin of the scan is usually taken as being at the base of the prostate where it meets the bladder, and needles can be inserted to varying depths relative to this origin. The needles containing the seeds are guided accurately to the correct location using TRUS imaging.

The most common planning procedure involves two stages,⁸⁵ an approach which has been adopted in the European recommendations on permanent seed implantation published in 2000⁷⁸ with a supplement to this in 2007⁷⁹ and contains

Figure 2. Sagittal CT section with the prescribed dose distribution (7 Gy = 100%). The virtual treatment applicator consisting of an intrauterine tube and a ring is shown with active source positions superimposed on the inserted applicator, which contains an internal marker wire. The outlines of the high-risk clinical target volume and bladder and sigmoid organs at risk are also shown.

information on the DVH planning parameters for the prostate, urethra and rectum. In addition, similar guidelines have also been published by the ABS.⁸⁰ The first of the two-stage process is to acquire the prostate image data during a TRUS study. These data are then used in an offline planning procedure to produce a treatment plan. The patient then returns to the clinic a number of days later, where the setup is replicated and the seeds are implanted as per the treatment plan. More recently, with improvements in the available technology, the need to overcome some of the difficulties associated with the two-stage technique, such as matching the patient position and prostate shape change, have become increasingly important. The optimal planning method is therefore to use a single-stage process with interactive planning and dynamic dose calculation. During this procedure, the volumetric data are acquired in the same manner as the two-stage technique with the difference now that the plan is computed and implant performed during the same session. As the seeds are implanted, their actual position is updated and fed back to the planning system where the plan can be re-optimized.^{86,87} Using this interactive planning technique, it has been shown to produce better coverage of the prostate CTV.⁸⁸ The interactive planning technique and dynamic dose calculation, which have been carried out for a number of years, can be compared with the current paradigm in EBRT where adaptive planning is emerging using image-guided radiotherapy in an attempt to modify, correct and adapt the pre-calculated plan to the real situation at the time of treatment.

The standard planning tool for assessing the quality of the implant, which is recommended by the RCR, ABS and AAPM,^{89–91} is post-implant dosimetry. The aim of this planning exercise is to be able to assess and audit the quality of the implant. Since the main determinant of a successful treatment is to achieve the correct dose to the correct volume, quality indices, such as the D_{90} (the dose to 90% of the prostate volume) and the V_{100} (the volume of the prostate receiving 100% of the dose) are used. These indices are evaluated and used to assess whether, in the event of disease recurrence after treatment, failure could be attributed to poor patient selection or treatment technique. At present, CT-based post planning is used to carry out the quantitative assessment of the implant (Figure 3), and it has been demonstrated that implants not satisfying the minimum requirements for the D_{90} and the V_{100} are associated with a higher risk of biochemical relapse.⁹²

HDR boost and monotherapy

There are many similarities between HDR and LDR prostate brachytherapy techniques. The principal difference is, however, that the planning is carried out after all the needles have been inserted and is therefore a real-time procedure. In addition, as the radiation used is the more energetic iridium-192, it is possible to implant larger volumes with some needles placed in the seminal vesicles. Given also that larger doses per fraction are possible without seriously affecting normal tissues, the radiobiological advantages may be great if, as it has been suggested, the α/β ratio for prostate is low.^{93,94}

HDR was initially used as a boost in conjunction with hypofractionated EBRT for patients with intermediate- to high-risk

Figure 3. Axial CT scan of a prostate seed implant used for post-implant dosimetry showing the prostate and rectum contours and the prescription isodose.

disease, but, more recently, using this method as a sole treatment has been shown to produce good results.^{95,96} The GEC-ESTRO group have recently published an update on the recommendations for the treatment of localized prostate cancer with HDR brachytherapy.⁹⁷

The HDR boost technique has been systematically reviewed in a comprehensive article by Zaorsky et al.⁹⁸ The review shows that the standard EBRT dose varies among centres and is generally delivered as a total dose of 36–54 Gy in 1.8- to 2.0-Gy fractions to the GTV (*i.e.* the prostate, with or without the seminal vesicles); and the HDR boost is typically delivered as a total dose of 12–30 Gy in 1–4 fractions, also delivered to the GTV, which is typically the prostate alone. The review also shows that HDR brachytherapy potentially has some theoretical advantages in terms of the ability to dose escalate. In general, the higher the radiation dose, the greater the number of cancer cells destroyed. However, normal cells surrounding the tumour will also be destroyed, so there must be a limit to this dose increase. The possibility, using brachytherapy techniques, to conform the dose to the tumour much more precisely, allows higher doses to be delivered whilst minimizing the damage to the surrounding healthy tissue. This physical effect coupled with the emerging evidence that the α/β ratio for prostate cancer cells is low^{93,94} implies that high doses per fraction are more effective and, in addition, where the α/β ratio is low, dose escalation is a necessary requirement to offset the cell repopulation.⁹⁹ Within the planning system, setting up a series of dose constraints to the prostate and normal tissues, such as the urethra and the rectum, enables inverse optimization techniques to be employed.¹⁰⁰ This produces highly conformal dose distributions delivering a high dose to the prostate and significantly lower doses to the rectum and urethra. In 2011, a publication by the Canadian group, Morton et al¹⁰¹ made the HDR boost technique more attractive

to busy UK radiotherapy departments, as it proposed a single 15-Gy fraction of brachytherapy together with 37.5 Gy delivered in 15 fractions of hypofractionated EBRT as opposed to 32–39 fractions of EBRT alone. In addition, recent technological advances in the use of real-time ultrasound image guidance and inverse planning tools have allowed the treatment to be carried out in one procedure. This represents a significant improvement on the CT-based planning methods, obviating the need to recompute the plan before treatment to correct for needle movement and prostate oedema that occur between imaging and treatment. Further studies have shown the benefits of this technique.^{102,103}

It has been suggested,¹⁰⁴ for the radiobiological reasons previously described, that not only could HDR prostate brachytherapy be used successfully as a boost to supplement EBRT but there could also be a case for using HDR brachytherapy as the sole modality treatment for low-to-intermediate risk patients. HDR prostate monotherapy has more commonly been studied in a setting where the brachytherapy is delivered in several fractions,¹⁰⁵ however, a single fraction of 19- or 20-Gy HDR monotherapy is now being investigated and, if early data are confirmed with longer follow-up, may well become the treatment of choice for many men with localized prostate cancer. A recent publication by Hoskin et al⁹⁵ shows that single-dose HDR brachytherapy is feasible with acceptable levels of acute complications and suggests that tolerance may have been reached with the single 19-Gy schedule.

A current area of interest for using HDR techniques within the prostate is that of focal boosts.¹⁰⁶ This is a technique where, in addition to the standard practice of delivering the prescribed dose to the whole prostate, an additional boost dose is given to the dominant intraprostatic lesion (DIL), the region where studies have shown that tumour recurrence is more likely to occur.¹⁰⁷ With advances in high-tech multiparametric MRI (mp-MRI) methods, such as MR spectroscopy and dynamic contrast-enhanced MRI together with diffusion-weighted MRI, sensitivity and specificity of prostate cancer detection has improved greatly.¹⁰⁸ Studies have shown that tumour delineation using these techniques has successfully enabled a boost dose to the DIL of up to 150% of the prescription dose.^{109,110} To increase the dose to the identified DIL requires accurate delineation and also attention to the dose delivered to the OARs. A recent publication by a group from Leeds, UK¹¹¹ investigated the feasibility of using mp-MRI for tumour delineation and also how the focal boost dose is affected if a margin is added to the tumour region, to account for delineation and image registration uncertainties. They concluded that focal tumour boost technique is feasible and can be delivered without violating urethral and rectal dose constraints. This concept is very much in its infancy and additional clinical studies, and ultimately, large randomized controlled trials are needed to validate this approach.

HDR skin brachytherapy (simple two-dimensional vs complex three-dimensional planning)

The initial beginnings of brachytherapy lay in the treatment of skin cancer, shortly after the discovery of radium in 1898, when in 1901, a Parisian doctor used radium sulphate to successfully

treat basal cell carcinoma.¹¹² Of course, much has changed since those pioneering days, but the principle of applying a radiation source to the skin to kill tumour cells is still as valid today. Non-melanoma skin cancers are the most common among the Caucasian population,¹¹³ with almost 100,000 cases diagnosed in the UK alone each year. There are many different treatment modalities, including surgery, megavoltage X-rays and electrons and orthovoltage X-rays, but the inherent advantages of brachytherapy and the dominance of the inverse square law results in a rapid fall-off in doses beyond the tumour enabling skin lesions to be treated with tumouricidal doses, while sparing the sensitive, underlying structures.

The main clinical sites for treatment using skin brachytherapy are the hands, scalp, ears and facial tumours where cosmesis is of paramount importance. The treatment technique involves creating a single plane mould taken from an impression of the treatment site. By applying the Paris dosimetry system⁵⁶ for catheter placement, a series of parallel, plastic catheters, spaced between 10- and 15-mm apart depending on the area to be covered, are then laid in the mould. To improve the dose gradient through the lesion, the catheters are secured about 5–20 mm away from the patient surface. This choice of treating distance will depend on such factors as the surface curvature and the thickness and area of the lesion and is an important requirement in the geometrical arrangement as shown by the Manchester dosimetry system.³ The ability to attach surface catheters that follow the skin contour means that the dose distribution produced will conform to the region to be treated and the dose gradient over the surface can be minimized. The surfaces treated do vary considerably in their curvature. Often, this shape can be adequately approximated to a simple 2D flat plane, for example, the back of the hand. Large treatment areas of the scalp, where there is significant curvature in two directions, require more complex 3D planning techniques where the plan can be optimized to deliver the prescribed dose at the surface (or reference depth) using a series of calculation points created over the region to be treated. The effect of the curvature on the position of the prescription isodose was considered by Sabbas et al,¹¹⁴ who concluded that the effect was minimal when this curvature is not excessive (no more than 5 cm in radius). However, the curvature examined was in one direction only and therefore not strictly applicable to the multidirectional curvature of the scalp. Another study reported by Beddar et al¹¹⁵ also compared the 2D planar situation with the 3D curvature and noted a 19% underdose at 10 mm along the central axis caused by the applicator concavity. Furthermore, it has been reported by Raina et al¹¹⁶ that surface treatments result in an underdose owing to the lack of full scatter conditions, since, as previously noted, planning systems assume an infinite scatter environment surrounding the target volume and applicator. They suggest accounting for this effect by increasing the planning system dose by the appropriate amount depending on the treatment depth with the caveat that this correction for lack of backscatter should be based only on locally measured data. Alternatively, the application of bolus material over the treatment area can be used to create full scatter conditions. When treating highly curved surface moulds therefore, full 3D planning is required for accurate dosimetry, which may need adjustment for the lack of full scatter conditions.

HDR rectal brachytherapy (simple two-dimensional vs complex three-dimensional planning)

To improve the local control in locally advanced rectal tumours, there is an increased use of pre-operative radiotherapy or chemoradiotherapy. There is evidence that increasing the dose of radiation improves the local control, and brachytherapy can be used to achieve this.^{117–119} For radical treatments, a flexible multichannel applicator can be used with either simple 2D techniques using digital X-ray fluoroscopic imaging for planning or full 3D CT/MRI. The simple 2D technique is based on using the standard applicator geometry and prescribing to a distance of typically 10 mm from the applicator surface. The longitudinal positioning of the treatment length can be found from the X-ray image where localization seeds, inserted at the upper and lower tumour extents during the applicator insertion procedure, are used as guides relative to the applicator marker wires. In order to visualize and outline the tumour effectively, as has been previously described, CT and/or MRI is required (Figure 4). Once outlined, the relevant catheters adjacent to the tumour can be assessed and the dose optimized to this volume using standard planning techniques. To improve dose sparing of the contralateral rectal wall, a water stand-off balloon can be used that, when inflated, helps to fix the applicator in place, provides better contact between the rectal wall and the catheters in the region to be treated and moves the contralateral side away, thereby reducing the dose. A more conformal dose distribution is therefore possible with 3D planning, and DVH data can be reported for comparison. This technique has been reported by Vuong et al.¹²⁰

FUTURE DEVELOPMENTS IN BRACHYTHERAPY TREATMENT PLANNING

Radiobiology

As we have seen, brachytherapy treatments use different radioactive sources and treatment techniques and exhibit quite a variety of spatial and temporal dose distributions. Treatments can consist of single-fraction continuous LDR irradiations in the case of permanent seed implants to single- or multifraction HDR irradiations of different dose fractionations. The clinical impact of such variations should be carried out by consideration of the complex interplay between the dynamics of dose delivery

and the biological response of irradiated cells. Radiobiological models that enable the interacting effects of dose delivery with cellular biology to be accounted for, can potentially provide a useful clinical tool for comparing and optimizing the relative clinical effectiveness of different brachytherapy treatment strategies. These models have been used increasingly over the past decade in research settings.^{121–123} The challenges facing radiobiology in brachytherapy lie in a better understanding of the effect on normal and target tissues resulting from exposure to the wide ranging dose rates used and volumes treated in brachytherapy. The requirement for planning systems to allow the user to combine, radiobiologically, the dose distributions from the EBRT and brachytherapy for multimodality treatments is an important area for research and development, which could potentially lead to a better understanding of the clinical effectiveness of a treatment. There have been several publications reporting on the potential clinical usefulness of radiobiological summation of EBRT with brachytherapy,^{124–126} and this is certainly an area for further research. In IGBT of the cervix, for example, the total dose received by the tumour and OARs from the EBRT and brachytherapy treatments is required so that dose and treatment outcome comparisons can be effectively made between different institutions. In order to combine the doses from the two different treatment modalities, the doses to the tumour and OARs from the EBRT and brachytherapy have to be converted, radiobiologically, into 2-Gy equivalent doses using the appropriate α/β ratios of ten for the tumour and three for the normal tissue, and then added together. Recommended total dose levels to the tumour and OARs are given in the RCR publication.²² This capability should be made possible within treatment planning systems.

Dose calculation

As has been previously discussed, the dose calculation method most modern brachytherapy planning systems use follows the AAPM recommendations laid out in the TG43 and TG43 U1 formalism.^{15,16} This formalism is based on measured or measurable quantities either by TLD or MC methods, produced by a source in a uniform water-equivalent medium. Generally, the influence of tissue heterogeneity, external body contour or applicator material is ignored, as well as interseed attenuation and interapplicator shielding. As described by Rivard et al,¹⁷ the limitations of the current water-equivalent medium-based TG43 dose calculation method can be seen in five areas, namely differences between the absorbed dose to water and tissue, differences between the radiation attenuation in water and tissue, radiation interactions in the applicator material, differences between the radiation scattering for the data set acquisition and the patient treatment and subtleties in the differences between absorbed dose and kerma. In order to account for the differences, which are notably more pronounced for low photon energies (<50 keV), a variety of model-based brachytherapy dose calculation algorithms are being investigated and are beginning to be implemented in commercial treatment planning systems. The AAPM TG186 has laid out the current status and recommendations for the clinical implementation of model-based dose calculation methods in brachytherapy.¹²⁷ Deterministic solutions to solving the linear Boltzmann transport

Figure 4. Sagittal CT section showing the tumour outline and dose distribution for a multichannel flexible rectal applicator.

Figure 5. The axial dose distribution around a shielded applicator calculated by solving the linear Boltzmann transport equation. Courtesy of Varian® Medical Systems Inc., Palo Alto, CA. All rights reserved.

equation have been tested successfully^{128–130} and are relatively faster than MC simulations. One such solver called Acuros® (Varian® Medical Systems Inc., Palo Alto, CA) tested against MC and measurement¹³¹ has been implemented for iridium-192 dose calculations in the Varian Medical Systems Inc., treatment planning system (TPS) BrachyVision™ (Figure 5). Another model-based algorithm is called collapsed cone and has been available in external beam TPSs for a number of years and compares well with MC simulations.¹³² A brachytherapy version of this algorithm has been developed by Carlsson and Ahnesjö¹³³ and has been used to calculate the dose for sources in the range

of 30–662 keV. It has also been used to account for the effect of the presence of high atomic number materials.¹³⁴ Currently, this collapsed cone algorithm is being integrated in the Nucletron™ BV TPS (Veenendaal, Netherlands) Oncentra® (Nucletron, Veenendaal, Netherlands) Brachy. In addition to dose calculation, it is important for centres to follow national and international recommendations for the dose prescription and reporting such as those already mentioned,^{4–7,22,46,78} as without this standardization, it becomes very difficult to compare studies between different institutions. In brachytherapy, dose inhomogeneity is inherent, with potentially large, high-dose regions that are likely to lead to a corresponding increase in toxicity. The magnitude of this high dose–volume as well as the low dose–volume must be considered when evaluating the suitability of a treatment plan with strict adherence to the recommendations.

CONCLUSION

Brachytherapy is currently going through a period of renaissance and change with more complex techniques involving state-of-the-art imaging and planning. There are a number of aspects in the treatment process not addressed in this review, such as source calibration, *in vivo* dosimetry and quality assurance, all of which are significant and could be the subject of future articles. New brachytherapy treatments as described here are being introduced into clinical practice and together with robust clinical trials, which follow national and international treatment and planning recommendations, can help provide optimum use of the treatment techniques to benefit patient outcome. The use of 3D imaging is becoming a standard practice and the development of new dose calculation algorithms will provide a more accurate representation of the delivered dose, allowing retrospective dosimetric studies to revisit doses delivered to the target and OARs in relation to outcome.

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