THE DEVELOPMENT OF ADVANCED RADIOTHERAPY TREATMENT TECHNIQUES

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Abstract

Radiation therapy has come a long way in the last few decades from treatment planning based on orthogonal radiographs with large margins around tumours. Developments in imaging and radiation planning software have led to improved radiotherapy treatment techniques such as intensity modulated radiotherapy, rotational intensity modulated radiotherapy and stereotactic body radiotherapy. These radiotherapy treatment advances enable sculpted dose distributions, with the ability to monitor and adapt to changes in patient and tumour position during radiotherapy. The purpose of this paper is to review the recent advances in radiotherapy treatment delivery with reference to how this may improve outcomes for cancer patients treated with radiotherapy.

Radiotherapy is one of the most efficacious and cost-effective modalities for the treatment of cancer. Over the past decade there have been many attempts to increase its efficacy. Two basic strategies exist to achieve this. Firstly, reduce the treatment volume by sparing tissue not suspected of tumour involvement while irradiating the defined target volume at each treatment session. This strategy includes techniques of treatment planning and delivery of radiotherapy, but is also intimately linked to the ability to define the anatomical margins of the tumour and therefore is heavily dependent on advances in medical imaging. The second strategy is to increase the differential response between the tumour and normal tissue using chemotherapeutic drugs, biologic agents including radioprotectors, and genetic or proteomic techniques. This paper focuses on the advances in radiotherapy treatment techniques that may provide therapeutic gains in the treatment of cancer. The paper will also discuss some of the advances that have enabled the widespread use of highly conformal techniques, particularly stereotactic radiotherapy.

Three dimensional conformal radiotherapy

Historically, the ability to define tumour volume accurately and to tailor radiation dose to this volume has been a constant challenge for the radiation oncologist. The introduction of axial CT technology in treatment planning has allowed for increasingly more precise anatomic definition of tumour volumes and surrounding normal tissues.[1] Three dimensional radiation treatment planning systems have been available to most radiation oncology centres in Australia since the early 2000s.The importance of three dimensional CT-based treatment planning on tumour control and reduced treatment complications has been recognised in a number of subsites including lung cancer, prostate cancer and head and neck cancer.[2-4] It is now considered the standard to which new treatment techniques are compared.

Fixed gantry (static) intensity modulated radiotherapy

Since its introduction more than a decade ago, intensity modulated radiotherapy (IMRT) has spread to most radiotherapy departments worldwide for a wide range of indications,[5] and recently has become widely used throughout Australia. The basic principle behind IMRT is the use of intensity modulated beams, which are defined as beams that deliver more than two intensity levels for a single beam direction and a single source position in space. In simple terms, IMRT enables the dose of radiation to conform better to the three dimensional shape of the tumour by controlling, or modulating the radiation beam's intensity. IMRT is frequently chosen over non-modulated external-beam three dimensional techniques (known as non-IMRT) on the basis of studies showing better planning target volume coverage and better sparing of organs at risk.

Many publications discuss the advantages of IMRT. There is now compelling evidence that this technique improves patient outcome in a number of sites. In head and neck cancer xerostomia is one of the most debilitating long term side-effects of treatment resulting from the effects of radiotherapy on salivary flow, particularly from the parotid glands. There is evidence from randomised control trials in head and neck cancer, comparing IMRT techniques to non-IMRT techniques, showing that IMRT with its ability to spare the parotid glands, significantly reduces the incidence of xerostomia with resulting improvements in associated quality of life.[6,7]

In prostate cancer, there is clear evidence from randomised control trials of a dose response to radiotherapy above 68 Gy for local and biochemical control, the latter being a robust surrogate for disease control.[8-10] The rationale for using IMRT in prostate cancer is clear, in that dose escalation to the primary tumour can be achieved while securing safe doses to organs at risk (eg. rectum and bladder). Consistency in the findings of clinical comparative

studies and predictions from planning studies (external validity), allow the conclusion to be made that IMRT enables adequate dose escalation with unchanged or lower gastrointestinal and genitourinary toxic effects and unchanged or better sexual function.[5]

In gynaecological and breast cancer, non-comparative studies of IMRT suggest that this technique may reduce both the acute and late treatment related complications with radiotherapy. In breast cancer there are now a number of randomised trials showing that breast IMRT significantly reduces the development of severe moist desquamation and the probability of having late changes in breast appearance compared to non-IMRT techniques.[11,12]

There is also evidence in non-comparative studies that IMRT may reduce long-term sensorineural hearing loss in paediatric patients with brain tumours,[13] may allow safe dose escalation for patients with pancreatic cancer,[14] and allow less toxic treatment for patients with anal cancer.[15]

A recent meta-analysis collated data from 56 trials and showed that IMRT can reduce toxicities when compared to non-IMRT treatments.[16] Although data relating to overall survival and local control are inconclusive at this time, a reduction in toxicity is an appropriate outcome measure worthy of use as a benchmark for implementation of a particular technique. The evidence for its benefit in planning and non-comparative studies is so compelling that many clinicians consider it the standard of care in some tumour subsites.

Rotational (dynamic) intensity modulated radiotherapy

Rotational IMRT builds on the technology of fixed gantry (static) IMRT, but rather than the treatment being delivered by multiple static beams, it is delivered in one or multiple arcs of radiotherapy while the beam is being modulated throughout the arc.

Both Helical Tomotherapy and Volumetric Modulated Arc Therapy are rotational IMRT modalities. Helical Tomotherapy delivers intensity-modulated fan beams in a helical rotational pattern similar to a diagnostic CT scan. Volumetric Modulated Arc Therapy, by comparison, uses a conventional linear accelerator to deliver radiation in a cone-beam geometry with no couch movement during the treatment.

Both modalities achieve superior target dose quality in a range of tumour sites when compared to static IMRT and require lower radiation doses, with shorter treatment times than static IMRT. This results in a significant improvement in the efficiency of delivering complex IMRT treatments. These benefits have been established in head and neck cancer,[17] prostate cancer,[18] as well as complicated lung and spine treatments,[19] but it is likely that the greatest benefit of this technology is the shorter treatment time enabling greater patient throughput in already busy departments.

Proton radiotherapy

Although not currently available in Australia, proton radiotherapy is a technique that may enable better target volume coverage with significantly reduced normal tissue dose. This is due to the physical properties of protons in that they deposit very little energy as they pass through tissue, but deposit it at the 'Bragg peak,' which can be spread out to provide a uniform dose across the target volume and virtually zero dose deep to the target.[20] As such, most of the clinical advantages are when high doses are required to cure tumours but are adjacent to critical structures (eg. base of skull tumours and prostate cancer), but also where the effects of lower dose to a significant volume are important (eg. paediatric radiation oncology).

Stereotactic radiotherapy and stereotactic radiosurgery

Stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS) is an application of precise delivery of a single (SRS) or several (SRT) high dose radiotherapy treatments for non-invasive ablation of an intracranial lesion (typically less than three to four centimetres in maximum diameter). Conventionally, SRS/SRT is performed with the use of a stereotactic head frame that is fixed to the calvarium in order to provide rigid patient immobilisation during planning and treatment delivery. The doses of radiation are much higher than daily fractionated radiotherapy in order to ablate the target lesion (typically 12-24 Gy in a one day treatment and even up to 140 Gy for radiosurgical thalamotomy). SRS/SRT is delivered to a target localised in three dimensions based on CT and/or MRI imaging. Although SRT/SRS are not new technologies, in recent years, there have been rapid developments in computing and instrumentation that have revolutionised these techniques.[21] SRS delivery systems can be broadly categorised by the method of radiation delivery as either from a series of Cobalt-60 (^{60}Co) sources (Gamma Knife®) or from a single-source linear accelerator (linac). For institutions initiating a radiosurgery program, the choice of system will depend on a variety of factors including the relative caseload of malignant and benign disease.

Gamma Knife® SRS

The Gamma Knife®, invented by Swedish neurosurgeon Lars Leksell,[22] contains 192-201 cobalt-60 sources. Each source emits a beam of radiation, and all the beams converge to the point of intersection (isocentre) to deliver a "shot" of radiation. With scores of intersecting beams centred on the target, the radiation dose at the isocentre is very large and drops off rapidly within a few millimetres. Therefore, much of the brain receives a low dose.[21] The Gamma Knife® is a dedicated cranial SRS unit by virtue of its geometric design, and requires an invasive stereotactic head frame for localisation and immobilisation. The first Australian centre offering Gamma Knife® opened in 2011.

Linear accelerator (linac) based SRS

There are now a number of commercially available systems which enable SRS/SRT on standard linacs. Some of the difficulties with the early linac based SRS systems were the need for dedicated planning systems, retrofitted hardware, as well as the onerous quality assurance measures required during patient treatment. The initial limitations of linac based units were overcome by developments in treatment planning software and more recently linacs better designed for SRS have emerged.[23] The major

advantage of linac based systems is the versatility in the machine, in that it is still able to be used for all of the other requirements of a busy radiation oncology department. As a result, is widely available throughout Australia.

CyberKnife® SRS

The CyberKnife® Robotic Radiosurgery System began as a frameless alternative to existing stereotactic radiosurgery systems such as the Gamma Knife® and conventional linacs equipped with head frames and stereotactic beam collimators. In the original CyberKnife® configuration, a linac mounted on a robotic manipulator delivered many independently targeted (non-isocentric) and non-coplanar treatment beams with high precision under continual x-ray image guidance.[24] Although this can be used for standard fractionated radiotherapy, it is ideal for both intra- and extra-cranial stereotactic treatments. It is not currently available in Australia but is used widely in North America, Asia and Europe.

Stereotactic body radiation therapy

Stereotactic body radiation therapy (SBRT) is an external beam radiation therapy method that has been developed based on the principles of intracranial SRS, but to an extracranial target within the body using a single dose or a small number of fractions.[25] This has been enabled by technical advances integrating various imaging modalities into the everyday practice of radiotherapy directly at the linear accelerator. It requires significantly improved delivery precision over that required for conventional radiotherapy and standard IMRT. Due to the high target dose and steep dose gradients beyond the target, limiting or compensating for target movement during treatment planning and delivery are often required.

Lung SBRT

SBRT has gained much attention as a novel and promising treatment option for early stage non-small cell lung cancer and patients with solitary or low volume lung metastasis. The rational for the practice of SBRT is the finding that very high radiation doses are required to locally control non-small cell lung cancer, higher than achievable with conventional radiation techniques.[26] Lung SBRT has largely been used for smaller, peripheral lesions. It allows treatment with escalated radiation doses to the site of the primary tumour by optimal lung sparing accounting for breathing motion compensation and image-guidance. This has resulted in increased local tumour control which, based on a number of prospective phase II trials, ranges consistently between 84-98%.[26-28] Lung SBRT is now being evaluated for patients with low volume metastatic lung disease.[29]

Spine SBRT

SBRT is an emerging technology in the multidisciplinary management of benign and malignant spinal/paraspinal tumours.[30] The spine is an ideal site for SBRT due to its relative immobility and potential clinical benefits of high dose delivery to optimise local control, given that disease progression can often result in spinal cord compression. Spinal SBRT is largely used for metastatic disease to the spine and aims to improve on existing rates of clinical response (eg. pain relief), tumour control, and to reduce re-treatment rates by delivering high biologically effective doses per fraction. Tumour doses typically range from 16 to 24 Gy in a single fraction or 6-9 Gy by three fractions, which are significantly greater than current palliative radiation oncology practice.[31]

The role of SBRT in metastatic spine tumours is being evaluated in a randomised trial by the Radiation Therapy Oncology Group (protocol 0631) for patients with significant pain and no history of radiation or surgery. The aim of the trial is to compare pain response after delivery of 16 Gy in a single fraction by using SBRT to delivery of 8 Gy in a single fraction with conventional radiation. However, it does not address the role of higher-dose SBRT in patients who have not received radiotherapy, in patients with previously irradiated spinal metastases or in postoperative patients.

Liver SBRT

With the emergence of SBRT techniques for both lung and spine disease there has been renewed interest in the use of radiotherapy for both primary and secondary disease of the liver.[32,33] The clinical experience in both primary and metastatic disease of the liver is emerging, with phase I and II trials demonstrating excellent local control and occasional long-term survivors. With appropriate patient selection and sparing of the uninvolved liver, serious toxicity can be avoided.[32]

Future directions

The advances in radiotherapy over the last few decades have been numerous and this article only addresses those relating to treatment techniques. The advances described would not have been possible without the availability of faster, more powerful computer systems that enable the efficient running of the advanced softwares required for planning and delivery. These systems have enabled advanced treatment delivery techniques to be planned and delivered in a timely fashion. With the evidence of improved outcomes for patients treated with IMRT, investment in the ability to utilise this technology for a larger number of patients, as is possible with fixed gantry and rotational IMRT, is required.

These advanced techniques require precise methods of targeting delivery, emphasising the importance of image-guided radiotherapy, another topic in this edition of *Cancer Forum.* The cost of these advanced techniques include increased training requirements for physicians and therapists, the need for powerful and efficient computing to manage all of the data and the complex and increasing nature of physics quality assurance measurements. It is likely that the role of the physicist in radiation oncology departments will increase due to the complexities of these treatment techniques.

As previously discussed, another powerful way to improve the therapeutic ratio in treating cancer is by using chemotherapeutic drugs, biologic agents including radioprotectors, and genetic or proteomic techniques. There is little known about the interaction of targeted therapies and radiotherapy. Through collaboration with our medical oncology colleagues, there will be

increased interest in investigating the role of these agents in concurrent or adjuvant use, combined with these advanced techniques, particularly SBRT.

Finally, although these rapid developments in radiotherapy delivery will continue to occur, it is paramount that we evaluate them adequately prior to considering their routine use. However, it may also need a rethink of the way in which we evaluate the benefit of a new treatment technique. As overall survival advantages are often difficult to detect, consideration of treatment toxicity, the number of treatment visits (treatment burden) and the ability to provide this technique to a larger population by improving efficiency, needs serious consideration as outcomes worth pursuing.

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