RECENT DEVELOPMENTS IN THE TECHNOLOGY OF RADIATION ONCOLOGY

A. Introduction

The accurate targeting of tumours with maximal sparing of normal tissues has been the foremost goal of radiotherapy practice. Over the past two decades, the ability to achieve this goal has improved greatly through advances in imaging technology, specifically the development of computerized tomography (CT), magnetic resonance imaging (MRI), positron-emission tomography (PET) and fusion PET/CT [I-1].

Developments in imaging technology coupled with advances in computer technology have fundamentally changed the processes of tumour targeting and radiation therapy planning. The ability to display anatomical information in an infinite selection of views has led to the emergence of three-dimensional conformal radiotherapy (3D-CRT); a modality in which the volume treated conforms closely to the shape of the tumour volume.

During the past decade, the leap in radiotherapy technology has been overwhelming. The present report presents an overview of recent developments in radiotherapy technology.

B. Recent technological advances

B.1. Intensity modulated radiation therapy (IMRT)

Intensity modulated radiation therapy (IMRT) is a sophisticated type of three-dimensional conformal radiotherapy that assigns non-uniform intensities to a tiny subdivision of beams called beamlets. The ability to optimally manipulate the intensities of individual rays within each beam leads to greatly increased control over the overall radiation fluence (i.e. the total number of photons/particles crossing over a given volume per unit time). This in turn allows for the custom design of optimal dose distributions. Improved dose distributions often lead to improved tumour control and reduced toxicity in normal tissue [I-2].

When a tumour is not well separated from the surrounding organs at risk and/or has a concave or irregular shape, there may be no practical combination of uniform-intensity beams that will safely treat the tumour and spare the healthy organs. In such instances, adding IMRT to beam shaping allows for much tighter conformity to targets. IMRT requires the setting of the relative intensities of tens of thousands of individual beamlets comprising an intensity modulated treatment plan. This task cannot be accomplished manually and requires the use of a multileaf collimator (MLC) [I-3] and specialized computer assisted optimization methods.

During the International Conference on Advances in Radiation Oncology (ICARO) organized by the IAEA in April 2009 [I-4], a debate was held on “IMRT: Are you ready for it?” with panel members who represented various views from all regions of the world. Health economics was identified as a key driver in the adoption of IMRT as a treatment modality. Nevertheless, there is still a lack of randomized trials that clearly demonstrate the clinical benefits of IMRT in many tumour sites other than improved dose distribution and a reduction in toxicity in some situations. Unexpected toxicities and recurrences have been reported in specialized literature on radiation oncology [I-1].

Advanced radiation treatment technologies such as IMRT require improved patient immobilization and image guidance techniques. There is some debate as to whether image guidance is always required with IMRT to ensure accurate delivery and whether it is required daily. This is due to the use of tighter margins around the tumour and the sharp dose fall-off with IMRT. Image guidance may be necessary in specific cases, such as when immobilization is not optimal or when hypofractionation is used. Other techniques to control organ motion during treatment such as respiratory-gating and breath-hold techniques may be necessary when reduced target volumes are considered.

Since IMRT sometimes uses more treatment fields from different directions, its use may increase the volume of normal tissue receiving low doses which might lead to a higher risk of secondary cancers. This is of particular concern in the case of paediatric patients. With the introduction of any advanced technology, such as IMRT and image guided radiation therapy, data should be collected in advance to allow a thorough evaluation of cost-effectiveness and cost-benefit.

Experts advise caution in the widespread implementation of these new technologies [I-4]. If the identification of target tissues is uncertain when margins around target volumes are tight, the likelihood of geographical misses or under-dosing of the target increases.

B.2 Image guided radiation therapy (IGRT)

IGRT is a technology aimed at increasing the precision of radiotherapy by frequently imaging the target and/or healthy tissues just before treatment and then adapting the treatment based on these images. There are several image guidance options available: non-integrated CT scans, integrated X-ray (kv) imaging, active implanted markers, ultrasound, single-slice CT, conventional CT or integrated cone-beam CT [I-5].

Safety margins are used in order to account for geometric uncertainties during radiotherapy (patient movements, internal organ movements). In many cases, these margins include part of the organs at risk, thereby limiting dose increases. The aim of image guided radiation therapy is to improve accuracy by imaging tumours and critical structures just before irradiation [I-5]. The availability of high quality imaging systems and automatic image registration has led to many new clinical applications such as the high precision hypofractionated treatments of brain metastases and solitary lung tumours with real time tumour position corrections.

B.3 Helical tomotherapy

Helical tomotherapy is a modality of radiation therapy in which the radiation is delivered slice-by-slice (hence the use of the Greek prefix tomo-, which means "slice"). This method of delivery differs from other forms of external beam radiation therapy in which the entire tumour volume is irradiated at one time [I-6] (Fig. I-1). The overall treatment time is relatively short which is the main advantage of this method.

Radiation therapy has developed with a strong reliance on homogeneity of dose throughout the tumour. Helical tomotherapy embodies the sequential delivery of radiation to different parts of the tumour which raises two important issues. First, this method, known as ‘field matching’, brings with it the possibility of a less-than-perfect match between two adjacent fields with a resultant ‘hot spot’ and/or ‘cold spot’ within the tumour. The second issue is that if the patient or tumour moves during this sequential delivery, a hot or cold spot may result. The first problem can be overcome, or at least minimized, by careful construction of the beam delivery system. The second requires close attention to the position of the target throughout treatment delivery.

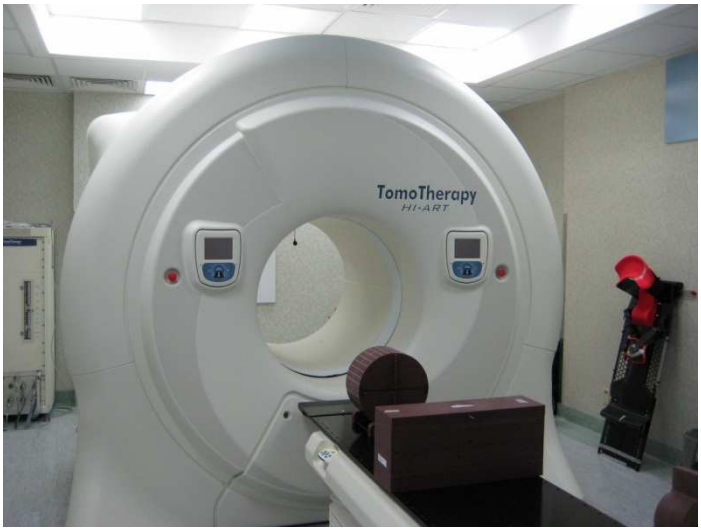

Figure I-1. Helical tomotherapy device.

B.4 Volumetric modulated arc therapy

Volumetric modulated arc therapy is a technique that delivers a precisely sculptured 3D dose distribution with a single 360-degree rotation of the linear accelerator gantry [I-7]. It is made possible by a treatment planning algorithm that simultaneously changes three parameters during treatment: (1) rotation speed of the gantry, (2) shape of the treatment aperture using the movement of multileaf collimator leaves, and (3) delivery dose rate.

Volumetric modulated arc therapy differs from other techniques such as helical tomotherapy or intensity modulated arc therapy (IMAT) in that it delivers doses to the whole volume, rather than slice-by-slice. The treatment planning algorithm contributes to the treatment precision helping to spare normal healthy tissue. The only downside of this technology is the high cost of the machine.

B.5 Stereotactic radiotherapy

Stereotactic radiotherapy (also called ‘radiosurgery’ although there is no surgery involved) consists of the delivery of a relatively high dose of radiation to a small volume using a precise stereotactic localization technique. The stereotactic component of the technique refers to the immobilization or fixation of the patient with a rigid head frame system that establishes a patient-specific coordinate system for the entire treatment process [I-8]. This modality is usually applied in the treatment of intracranial tumours. After placement of the head frame, typically by use of four pins that penetrate the scalp and impinge the outer table of the skull, an imaging study (CT, MRI) is performed to localize the target volume relative to the head frame coordinates.

Stereotactic radiotherapy can be delivered using a gamma knife device. This machine uses 201 small cobalt-60 sources collimated to converge in a small volume where the lesion is located.

A linear accelerator can be modified to perform stereotactic radiotherapy (Fig. I-2). The linear accelerator is modified to accept a tertiary collimator assembly to accurately position circular collimators to form small circular fields of 4 to 40 mm in diameter. The peripheral dose is spread over a large volume by using radiation paths that follow arcs. Stereotactic radiotherapy is continuously being improved and it remains a popular and increasingly used modality.

Small intracranial tumours in general, pituitary adenomas, small meningiomas, acoustic neuroma, craniopharyngioma, pineal tumours, brain metastasis or non-malignant conditions such as arterio-venous malformations are often treated with stereotactic radiotherapy. Stereotactic body radiotherapy is also being used to treat localized liver tumours.

Figure I-2. A linear accelerator commonly used in radiosurgery.

B.6 Robotic radiotherapy

Robotic radiotherapy is a frameless robotic radiosurgery system (Fig. I-3). The two main elements of robotic radiotherapy are the radiation produced from a small linear accelerator and a robotic arm which allows the energy to be directed towards any part of the body from any direction.

The robotic radiotherapy system is a method of delivering radiotherapy with the intention of targeting treatment more accurately than standard radiotherapy. Owing to its high cost, it is not widely available, although the number of centres offering the treatment around the world has grown in recent years to over 150, particularly in North America, East Asia and Europe. The robotic radiotherapy system is used for treatment of malignant and benign tumours, as well as other medical conditions.

Figure I-3. Robotic radiotherapy unit.

C. Challenges in radiotherapy and ways to address them

C.1 The fourth dimension: time and movement

Radiation oncologists face particular problems in treating parts of the body where organs and tumours may move during treatment. Movement of the target due to respiration or for any other reason during treatment increases the risk of missing the targeted area or under-dosing the area. As the delivery of the radiation dose becomes more and more precise, movements of organs and tumour have a significant effect on the accuracy of the dose delivery. This is particularly dramatic for tumours located in the chest, since they move during breathing. However, movement is not only an issue with tumours located in the chest; tumours in the larynx, abdomen (liver), prostate and bladder,21 and in the pelvis in general also move during and between treatment applications.

As a result of the development of respiratory-gated radiotherapy during the last five years or so, tumour motion can now be taken into account very precisely [I-9]. In computer-driven respiratory gated radiotherapy, a small plastic box with reflective markers is placed on the patient's abdomen. The reflecting markers move during breathing and a digital camera hooked to a central processing unit monitors these movements in real time. A computer programme analyses the movements and triggers the treatment beam synchronized with the respiratory cycle. With this technique it is also possible to choose the respiratory phase; depending on its location, the tumour can be irradiated during inspiration or expiration. Therefore, the tumour will always be encompassed by the radiation beam but excessive exposure of critical organs will be avoided.

C.2 PET in radiotherapy treatment planning

Recent years have seen an increasing trend in the use of positron emission tomography (PET) and PET/CT imaging in oncology. Along with diagnosis, staging, relapse detection and follow-up, one of the main applications of PET/CT is the assessment of treatment response and treatment planning. PET provides molecular information about the tumour microenvironment ("functional imaging") in addition to anatomical imaging. Therefore, it is highly beneficial to integrate PET data into radiotherapy treatment planning. The use of functional imaging to better delineate the treatment target is a good example of individualized treatment. In fact, instead of using a previously established field or set of fields, the radiation dose is shaped on the tumour for each individual patient [I-10].

PET/CT radiotherapy treatment planning is an evolving strategy which presents some obstacles that need to be addressed. The use of PET for target volume delineation requires specific tuning of parameters such as image acquisition, processing and segmentation and these may vary from one tumour site to another. This is currently the topic of intensive research work.

C.3 Particle therapy: proton beam and heavy ions

There is an increasing use of particle therapy in the field of radiation oncology with increasing focus on the application of proton beam therapy. According to data from the Particle Therapy Co-Operative Group, as of March 2010 there are 30 proton therapy centres in operation worldwide, and more than 67 000 patients have been treated with this therapy. The number of operating proton centres is projected to double in the near future.

The advantage of particle therapy, including proton therapy, is that the particle beam can provide a more precise dose distribution compared to photon beam (X-ray) radiotherapy. A particle beam deposits its energy at a certain depth as a sharp energy peak called Bragg peak, releasing a much lower dose before and almost none after this peak. Thus, by manipulating this characteristic, particle therapy can yield better dose distributions than photon therapy, providing the therapeutic dose to the tumour while minimizing unnecessary doses to healthy tissues [I-11, I-12, I-13].

One of the main issues surrounding the application of proton therapy is the lack of evidence on clinical benefit from comparative controlled clinical trials. While the superiority of the dose distribution of proton therapy has been clearly shown in physical studies on proton therapy, the clinical evidence comes mostly from phase II clinical studies or retrospective series.

Cost-effectiveness is another concern currently surrounding proton beam therapy. The implementation of proton therapy requires a sophisticated facility with accelerators such as cyclotrons or synchrotrons. Socio-economic cost-benefit analysis is required in order to demonstrate that proton therapy should be included as a part of standard cancer treatment modalities [I-14].

The main issues surrounding the application of proton and carbon ion therapy (Fig. I-4) are similar, namely the lack of evidence from randomized controlled clinical trials of the benefits of the therapy and the high cost. While conducting randomized controlled studies may be difficult for such a highly specialized treatment, objective outcome data analysis such as from a matched-pair controlled study, is warranted to assess the true benefit of particle therapy. The cost of implementing carbon ion therapy is even higher than the cost of proton therapy. While the effort to down-size the scale and cost of carbon ion therapy facilities is ongoing, a cost-benefit analysis would be necessary when considering the significant initial capital investment required.

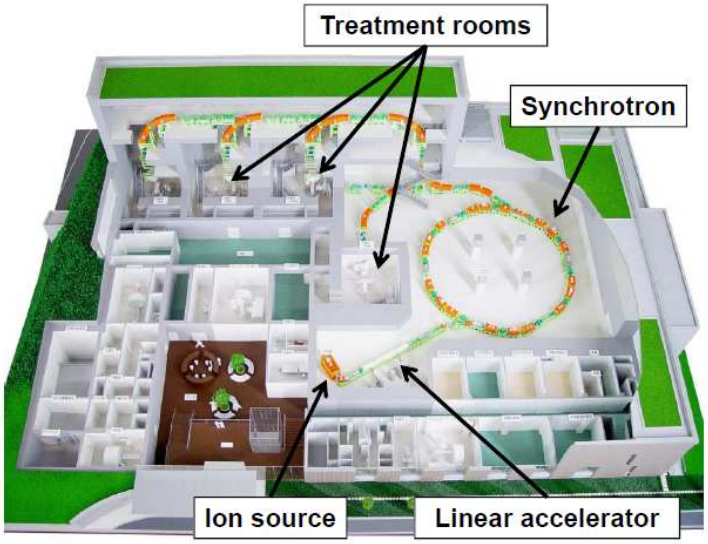

Figure I-4. Schematic diagram of carbon a ion therapy facility
(Courtesy of Gunma University Heavy Ion Medical Center).

C.4 Introduction of advanced technologies: the radiation oncologist perspective

The implementation of advanced radiotherapy technologies often leads to less personal contact between the physician and the patient. The radiation oncologist deals more and more with planning systems and dose–volume histograms (DVHs) and there is less interaction with the actual patient. This trend needs to be consciously counterbalanced by a more personal and holistic approach. This distance also makes it more difficult for the medical staff to intuitively understand the relationship between the radiation fields and the patient's anatomy. Whereas with 3D conformal radiation therapy the physician can rely on port films to assess the irradiated volume, with IMRT the physician must rely on tools such as computer simulations and DVHs. Users of advanced technologies should be cautioned not to become too dependent upon the technology itself. Experts generally recommend that advanced technologies such as IMRT/IGRT should not be acquired until physicians and other radiotherapy staff are fully experienced with treatment planning techniques in 3D conformal therapy.

Modern 3D approaches including IMRT introduce new requirements in terms of understanding of axial imaging and tumour/organ delineation. Recent literature points to an uncertainty level at this stage known as "inter-observer variations". Efforts continue to harmonize the criteria with which tumours, organs and anatomical structures are contoured by the radiation oncologist and how volumes are defined. The treatment of tumours in the head-and-neck region with IMRT also requires an initial process of learning for the treating team.

C.5 Introduction of advanced technologies: the medical physics perspective

The introduction of IMRT and stereotactic radiation therapy procedures brings special physics problems. For example, calibrations have to be performed in small fields where the dosimetry is challenging, and no harmonized dosimetry protocol exists. Use of the correct type of dosimeter is critical and errors in measurement can be substantial. Several new treatment machines provide radiation beams that do not comply with the reference field dimensions given in existing dosimetry protocols, thereby complicating the accurate determination of dose for small and non-standard beams.

The introduction of highly precise collimators (and their use in IMRT), small fields, robotics, stereotactic delivery, volumetric arc therapy and image guidance has brought new challenges for commissioning and quality assurance (QA). Existing QA guidelines are often inadequate for the use of some of these technologies [I-14]. The new technologies are developing at a historically high rate. New commissioning and QA protocols do not follow that pace. Increasingly complex QA procedures require additional staff in adequate numbers in the radiotherapy centres that actually implement the advanced technologies. New QA procedures are needed and are under development. In the meantime, the existing paradigm of commissioning followed by frequent QA should continue, with attention paid to the capabilities offered by the new technologies. Risk management tools should be adapted from other industries, to help focus QA procedures on where they can be most effective [I-14].

C.6 Brachytherapy

Brachytherapy is the administration of radiation therapy by placing radioactive sources adjacent to or into tumours or body cavities. With this mode of therapy, a high radiation dose can be delivered locally to the tumour with rapid dose fall-off in the surrounding normal tissues. In the past, brachytherapy was carried out mostly with radium or radon sources. Currently, the use of artificially produced radionuclides such as caesium-137, iridium-192, gold-198, iodine-125 and palladium-103 is rapidly increasing.

According to the definition of the International Commission on Radiation Units (ICRU) [I-15], high dose rate (HDR) brachytherapy means more than 12 gray per hour (Gy/h), although the usual dose rate delivered in current practices is about 100–300 Gy/h. The use of HDR brachytherapy (Fig. I-5) has the advantage that treatments can be performed in a few minutes allowing them to be given in an outpatient setting with minimal risk of applicator movement and minimal patient discomfort. Remote controlled afterloading brachytherapy devices eliminate the hazards of radiation exposure.

A recent development in the field of HDR brachytherapy is the miniaturization of cobalt-60 sources into microsources that are the same size as a HDR iridium-192 source. These new systems have the same versatility of all modern afterloading HDR systems but with the added advantage of using an isotope with a half-life of 5.27 years. This makes it possible to replace the source only every 5 years instead of every 3–4 months as is the case with iridium-192. The savings in terms of resources, time and procedures are significant [I-16].

Currently, the image-based treatment planning of gynaecological brachytherapy takes full advantage of modern imaging techniques (CT, MRI) to visualize the tumour, the applicators and the organs at risk and prescribes the doses accurately to pre-defined volumes and with dose–volume constraints [I-17].

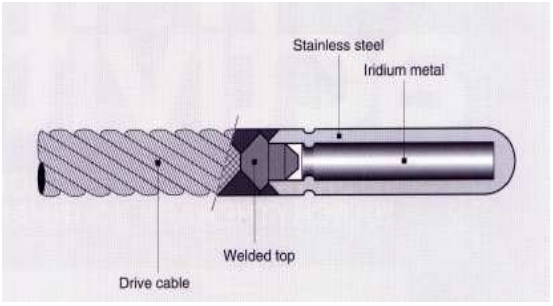

Figure I-5. High dose rate brachytherapy microsource (Courtesy of Nucletron)

C.7 Challenges in the introduction of new technologies

The potential or actual use of new advanced technologies raises questions about cost, efficacy and ethics. The increased capital and operating costs and the economic burden of increased QA is a challenge [I-14]. Stereotactic radiosurgery, stereotactic body radiation therapy (SBRT), proton and other charged particle therapies using single or hypo-fractionation regimens have the advantage of saving time but require well-qualified personnel and excellent QA/QC programmes, as there is little chance of adjustment once the treatment has been initiated.

The major challenges for using technically advanced equipment and techniques are: appropriate human resources, qualified and trained staff for the accurate delivery of high therapeutic radiation doses; infrastructure requirements capable of handling this technology most efficiently and effectively; types and stages of cancers to be treated; development of commissioning and QA/QC protocols; and institutional resources and clinical backup to deal with increased downtime for the more complex technologies [I-19].

Advanced technological needs for radiation oncology must be considered in the context of the needs of the countries concerned in terms of essential infrastructure in order to allow for a smooth, incremental and safe progression to advanced radiotherapy services.

An important theme echoed by experts is the global shortage of skilled professionals [I-2, I-10]. It is noted that while short-term and local solutions have been devised, there is a need in many countries for a long-term strategy to establish training programmes and produce trainers and educators who could increase the availability of adequately trained staff in the radiotherapy disciplines. Training must be adapted to both the working environment and the available technology; little benefit is derived by a trainee or the trainee's institution when the education addresses a technology not available in his or her own country.

There is clearly a role for networking on the national and regional levels to support local education programmes.

SUMMARY

Recent technological developments in radiation oncology have resulted in better dose distributions and reduced toxicity in selected tumour sites which may in turn lead to potentially higher chances of local tumour control and improved cure rates. This is one of the reasons why these treatments have become more popular among radiation oncologists and hospital administrators. However, increased revenues of IMRT and other new technologies may lead to their overutilization. The clinical scientific evidence regarding local tumour control and overall cancer survival for most tumour sites are generally inconclusive at this time.

Additionalt clinical trials are necessary to demonstrate the benefits of advanced technologies before they are adopted for widespread use.

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