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Intensity Modulated Radiation Therapy: Review and Preview

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Abstract

Intensity modulated radiotherapy represents a significant advance in conformal radiotherapy. In particular, it allows the delivery of dose distributions with concave isodose profiles such that radiosensitive normal tissues close to, or even within a concavity of, a tumour may be spared from radiation injury. This article reviews the clinical application of this technique to date, and discusses the practical issues of treatment planning and delivery from the clinician's perspective.

Keywords: radiation, conformal, therapeutic, adjunct, multileaf collimator

Introduction

Intensity-modulated radiotherapy (IMRT) differs from standard external radiotherapy techniques as it provides the ability to more accurately irradiate the cancerous tissues.

It allows sparing of organs at risk that are surrounded by targets with concave surfaces. In IMRT this is achieved by controlling – or modulating - the intensity of the subcomponents of each radiation beam. IMRT can be produced through numerous delivery methods, using a multileaf collimator (MLC) with its leaves moving or not with the radiation on, or with a gantry moving with the treatment beam on as e.g. in tomotherapy.[1]

Before radiotherapy can be delivered computed tomography and other images are used by the clinician to carefully delineate both target tissues and tissues at risk. Treatment planning software is then used for dose-volume histogram calculations. The high degree of accuracy can only be maintained with IMRT if one corrects, sometimes using daily imaging, for set up errors or for internal organ motion.As the process of IMRT implementation and delivery is very complex it requires access to appropriately trained experts in radiation physics and dosimetry. Careful quality assurance is necessary at every step of the process.

IMRT is a form of conformal therapy that combines several intensity modulated beams. The resultant isodoses are highly conformal and, uniquely, can yield a concave distribution .IMRT therefore offers a significant advance in conformal therapy [1], by improving conformality and reducing radiation dose to radiosensitive normal tissues close to the tumour even if they lie within a concavity in the PTV [2]. In radiotherapy there are many clinical situations where radiosensitive normal tissues lie within a concavity surrounded by the PTV. Treatment of patients

with tumours of the larynx, pharynx or thyroid offers a good example. The clinical target volume (CTV) often includes a midline target and bilateral cervical lymph nodes, producing a horseshoe-shaped PTV with the spinal cord within the concavity [3]. Homogeneous irradiation of these PTVs to radical doses (50±66 Gy) with conventional external beam radiotherapy is difficult. Typically, parallel-opposed photon portals are matched to electron beams. This technique leads to dose inhomogeneity at the photon±electron matchline, and also underdoses the posterior cervical lymph nodes close to the spinal cord [4]. This shape of PTV can be treated homo- geneously using IMRT without the need for electrons. The dose to the spinal cord can be kept well within tolerance [4,5] and permits tumour dose escalation. Significant normal tissue sparing using IMRT has also been demonstrated in planning studies for tumours of the maxillary antrum, nasopharynx, lung and prostate [5,6,7]. Complex dose distributions can be delivered that avoid a number of radiosensitive normal tissues close to a tumour. For example, in the treatment of nasopharyngeal cancer, large parallel-opposed lateral portals are used to encompass macroscopic disease and sites of occult metastases. With this technique parotid glands, spinal cord and brainstem are inevitably included in the irradiated volume although these structures do not need to be included in the target volume. Complete xerostomia and risk of myelopathy are the result. By defining concavities in the PTV, IMRT can produce a dose distribution that reduces the radiation dose to these organs and this promises a significant reduction in treatment morbidity. IMRT could be used for the whole duration of a radiotherapy treatment, or simply as a boost after more conventional treatment. The appropriateness of these two approaches is likely to depend on the tolerance doses of surrounding radiosensitive normal tissues.[6,7]

Clinical applications of IMRT

Breast Cancer

RT is well established as a treatment for early breast cancer patients. Studies report that RT results in both increased local control of the cancer and increased survival rates. IMRT has had a major role in limiting acute and chronic toxicity and improving the quality of life for women who receive RT. [8,9]

Head & Neck Cancer – Nasopharynx

Nasopharyngeal cancer is endemic in China and Southeast Asia. The standard of care is a combination of chemotherapy and RT [10]. The toxicities of RT and concurrent chemotherapy are often severe, causing delays or dose reductions during chemotherapy, interruptions of RT, and diminished QOL for patients. When toxicities force alterations in the planned therapy, this can lead to decreased cancer control. The use of IMRT has substantially decreased these toxicities, and decreased interruptions in planned therapy.

The principle results of studies that looked at IMRT as compared with earlier forms of RT for nasopharyngeal cancer patients showed decreased normal tissue toxicity and improved local control of cancers. These results are not likely to be unique to nasopharyngeal cancer patients because the cancer biology, pathology and staging are similar in other cancer sites.

Head & Neck Cancer – Oropharynx

A phase III multicenter trial (PARSPORT) in the United Kingdom compared IMRT to 3-D CRT in the treatment of pharyngeal cancer patients [11]. The percentage of 3-D CRT patients experiencing grade 2 or worse xerostomia was 64%, compared with 41% from the IMRT group – a statistically significant difference.

A retrospective study [12] compared the toxicity and the efficacy of 3-D CRT and IMRT administered to patients who were also receiving chemotherapy for locally advanced cancer of the oropharynx. The results after three

years of follow-up give significantly improved overall survival, disease free survival, and locoregional control of the tumor with IMRT [12].

French physicians did a matched pair analysis of head and neck patients treated with IMRT vs. 3-D CRT [13]. They studied 67 pairs of patients. Using validated QOL questionnaires, they reported statistically significant improvements in QOL for patients treated with IMRT, including less dry mouth, sticky saliva, mouth pain, jaw pain, and swallowing and eating difficulties. Xerostomia greater than grade 2 occurred in 67% of the 3-D CRT patients and in only 12% of the IMRT patients. There were no differences in cancer control outcomes.

Lung Cancer

Several physics and dosimetry studies have compared 3-D CRT and IMRT treatment plans for the treatment of locally advanced lung cancer (i.e. stages III and IV). The resulting dose distributions and dose volume histograms show better sparing of normal tissues with IMRT. The IMRT plans, delivered lower doses to the healthy lung, esophagus, heart, and spinal cord.[10,14,15]

Several clinical studies report that higher doses of RT delivered to the cancer result in improved local cancer control [16,17]. Since IMRT makes it possible for physicians to deliver higher doses without causing commensurate levels of toxicity in healthy tissues, future studies may show greater treatment efficacy with IMRT. Current clinical trials are designed to evaluate whether IMRT can deliver higher doses while holding toxicity to acceptable levels. The outcomes that these studies are designed to measure include local cancer control, toxicity, and QOL.[16,17]

Prostate Cancer

The studies reported to date comparing 3-D CRT with IMRT in the treatment of prostate cancer are not controlled trials, but are retrospective comparisons of 2 cohorts of patients treated in different years. Some studies use a “matched pair” form of analysis.

All of these studies concern “early stage” patients. The definition of early stage varies, and involves age, tumor stage, PSA value and Gleason score. Because of these differences, the studies can be somewhat difficult to directly compare. Some also use different criteria for evaluating PSA control as an endpoint. IMRT in the treatment of prostate cancer is used for two clinical aims: reduction of treatment toxicity and improvement in disease free survival (DFS). In the quest for higher rates of DFS, some centers have used IMRT to escalate the dose to the prostate, delivering doses that would produce unacceptable levels of toxicity using 3-D CRT. Other centers choose to stay with lower doses, and use IMRT only to reduce toxicity. Some level of urinary toxicity from RT to the prostatic urethra, which runs through the center of the prostate, is unavoidable.

Several randomized trials demonstrate that higher doses of 3-D CRT produce a better DFS rate [18, 19]. The Fox Chase Cancer Center experience with prostate cancer patients shows a dose response for doses from less than 72 Gy to greater than 76 Gy [20]. IMRT makes it possible to deliver doses that are higher (≥80 Gy), and there is evidence that these higher doses produce even longer DFS, especially in low and intermediate risk patients.

Conclusion

IMRT has made an amazing development from its first conception in the early 1980s to today’s widespread clinical application in some countries. While today’s clinical implementation of IMRT may be driven in part by economic incentives, its original development most certainly was not. It is one example where physicists, supported by mathematicians and computer scientists, have made a major impact on medicine, in this case on the daily clinical practice in radiation oncology. IMRT

continues to be an area of active research and development. Future developments have the potential to lead to further substantial and clinically relevant improvements.

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