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Review Article

A review on Intensity Modulated Radiation Therapy (IMRT) in cancer treatment

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Abstract: Intensity Modulated Radiation Therapy (IMRT) has been buzz word in radiotherapy technology for more than a decade. The technology as such, and their application, has been evolving significantly over this time and it is interesting to have an attempt at taking stock. Due to the increase in the utilization of IMRT over the last decade, the complexity of IMRT to plan and administer, and because at first, there was limited published clinical data, some have criticized IMRT as expensive medicine with uncertain benefit. This handout provides an overview of recent data related to the clinical effectiveness of IMRT and describes studies that are currently underway so the reader will understand the reasons for increased adoption of IMRT. A key question regarding IMRT is whether IMRT is cost effective. The cost is higher than other forms of RT, mostly due to increased physician and other staff time. The additional time spent in planning and delivering IMRT is now a necessary part of maintaining accuracy. Better cancer control occurs when higher doses of RT or better combinations of RT and chemotherapy are possible. This is supported by data in the treatment of head & neck, lung and prostate cancer.
Keywords: IMRT, clinical data, radiation therapy.

INTRODUCTION

IMRT is the most exciting technological and conceptual advance in radiotherapy since the introduction of CT based dose planning in late 1970's. The benefits of IMRT are correlated to dose escalation, potential for improved locoregional control and anticipated superior treatment results. However most compelling justification for this expensive time consuming modality is established ability of normal tissue sparing and improved quality of life. These features make IMRT the treatment of choice in clinical situations where there is a clear cut relationship between dose delivered and clinical response and where normal tissue provide a constraint on its delivery. This is especially applicable to head and neck cancers where it is being widely applied. A few other common tumor sites that may fit into this category include carcinoma prostate, cervix and breast [1-9].

IMRT is a type of external beam radiation therapy that permits complex three-dimensional shaping of the radiation beams to precisely target the tumor. This allows for a larger dose of radiation to be applied to the tumor site, while minimizing exposure of the surrounding healthy tissue. Instead of a single, uniform beam as in traditional external beam radiation, IMRT involves the delivery of many small beams of varying intensity. Computer algorithms are used to coordinate the beams and plan the delivery of the radiation dose. Compared to other types of external beam radiation, IMRT is best able to generate concave dose distributions.

IMRT is a newer method of delivering radiation to target structures that differs from traditional methods of radiation delivery. The basis of IMRT is the use of intensity-modulated beams that can provide two or more intensity levels for any single beam direction and any single source position [10]. Through this mechanism, IMRT treatment plans are able to generate concave dose distributions and dose gradients with narrower margins than those allowed using traditional methods [10, 11]. This fact makes IMRT especially suitable for treating complex treatment volumes and avoiding close proximity organs at risk (OAR) that may be dose limiting [10]. As a consequence, IMRT theoretically may provide benefits in terms of increased tumor control through escalated dose and reduced normal tissue complications through OAR sparing. It must be noted that as total radiation dose delivered via IMRT would be the same as the total radiation dose given via any other method of radiation therapy, no difference in disease-related outcomes would be expected. The main benefit expected with IMRT is a reduction in adverse event rates, especially those associated with radiation damage to nearby OAR.

Radiation delivery is also more complex, requiring specialized software to automate the process, in an attempt to reduce treatment time and risk of delivery error. In addition, as the precision of radiation delivery increases, so does the need for accurate daily patient positioning [12]. This increased complexity has significant resource implications for radiation departments, demands that have been identified in a previous Cancer Care Ontario (CCO) document [13].

ADVANTAGE OF IMRT

Highly conformal dose distribution

The improved ability to deliver highly conformal radiotherapy with IMRT gives new hope for dose escalation to improve local control and cure with radiotherapy. It is especially valuable when the target is in close proximity to the organs at risk. A perfect case for IMRT is head-and-neck cancer, which most likely will benefit from IMRT because (a) local failure remains a major problem for head-and neck cancers, (b) a demonstrated dose response exists, and (c) the complexity of the anatomy, with dose-limiting critical structures such as spinal cord and salivary glands in close proximity to the target, and (d) better immobilization without internal motions of the target. Nasopharyngeal carcinoma is a good example for this improved radiotherapy technology in light of its location, proximity to a number of critical structures, and complexity of tumor contour (commonly concave shape). The lack of effective salvage treatment for local recurrence leaves no room for error of primary radiotherapy. The high cure rate with radiotherapy mandates a lower threshold of tolerance for long-term, potentially debilitating complications or squealed of radiotherapy. Preliminary data have shown promising results that IMRT can improve tumor target coverage with excellent local control and significant sparing of normal tissues. It could be a major advance in the treatment, and become the standard of care for this disease [14-16]**.**

Differential dose distribution and multiple targets

The ability of IMRT to perform differential dose delivery to multiple separate targets of interest has enabled the new concept of altered fractionation, such as simultaneous modulated accelerated radiation therapy (referred to as SMART fractionation), in an effort to shorten the overall treatment time to overcome accelerated repopulation and to increase efficacy on tumors by increasing the dose per fraction**[17].** Differential dose distribution within the target(s) would allow a tailored dose based on tumor burden (gross vs. microscopic) or relative radiosensitivity (hypoxic vs. oxic)

DISADVANTAGE OF IMRT

Dose inhomogeneity within the target

Dose inhomogeneity within the target is an unavoidable phenomena associated with IMRT. It is a tradeoff for higher conformality when multiple beams are used. Opposing beams create the best uniform dose distribution and coverage, but at the expense of nonconformality. When we evaluate a treatment plan and its dose distribution, it is critical to pay attention not only to the coverage, but also to the dose gradient in the target. To achieve an adequate coverage of the intended target with IMRT, often have to choose 80% or lower isodose line for dose prescription. This implies that there must be at least 20% higher dose somewhere in the target. It is difficult to avoid such dose heterogeneity in the target, and its impact on probability of tumor control remains unknown and needs to be investigated. Intuitively, dose inhomogeneity within the target may have potential advantage when the "hot spot" falls in the center of the tumor, where the most tumor burden and hypoxic cells are found. However, "hot spot" in the target can also cause significant undesirable effects when it overlaps normal tissues. It could be more problematic for a postoperative case when the intended target is microscopic disease located within normal tissues.

Increased volume of normal tissue exposure

It is a rule rather than exception that the normal tissue volume being exposed to radiation with IMRT is much larger than that exposed during conventional external beam arrangement. The dose delivery with IMRT is basically redistributing or spreading the normal tissue dose to less critical areas in order to reduce the dose to the tissues at risk. This is especially true when tomotherapy-based IMRT is used. Therefore, IMRT may offer a better dose distribution around the target, but at the cost of increase in volume of normal tissue exposure.

Inefficiency in beam delivery/beam leakage

IMRT is an inefficient radiation delivery process and requires enormous amount of output or monitor units to compose intensity-modulated beam segments. The majority of monitor units, which could increase by as much as 90%, are wasted. IMRT not only increases the workloads for the machine, but also increases the amount of leakage radiation in the treatment field due primarily to beam transmission and leakage. As a result, the amount of total body dose could be substantially higher than the dose from conventional external beam irradiation. It has been reported that for a typical head-and-neck field, the dose to the whole body could be larger than 50 cGy or 500 mSv[18,19]. It becomes critical when we are concerned about radiation-induced malignancy.

Prolonged treatment delivery time

Another potential disadvantage of IMRT is increased treatment time, which is inherent to the inefficiency of beam delivery. A prolonged treatment time could decrease the patient's tolerance and increase the potential for intra-fraction movement of the patient. For example, if a patient needs to be immobilized under

a tight face mask with an intra-oral positioner in place for a head-and-neck cancer, the patient may have difficulty in tolerating daily treatment without interruptions (sitting up for spitting or swallowing, etc.) during each treatment delivery. For a pediatric patient who needs daily general anesthesia for radiation therapy, a prolonged treatment time will also require a longer anesthesia time, that could potentially increase the risks associated with general anesthesia.

Technique available

The purpose of IMRT is to produce a three dimensional dose distribution within a patient. In principle beams of radiation can be projected from any direction but initially, to distinguish between two separate classes of techniques, only coplanar beam directions will be considered. It is also necessary, for this discussion, to distinguish between a technique, an arrangement of beams which when added together produce the required three dimensional dose distribution, and a delivery method describing the way in which the radiation from a particular beam direction is modulated. A technique consists of a series of beam directions each defined by the linear accelerator gantry angle. From each beam direction a modulated beam is projected towards the isocentre. The beams can be narrow fan beams, modulated in one dimension or divergent cone beams modulated in two dimensions.

IMRT for Head and neck Cancer

Head and neck, while an uncommon tumor site, is an important site in radiotherapy for several reasons. First, as IMRT has become widely used in the head and neck to decrease the substantial radiation-related toxicities, preliminary clinical outcome data are emerging from this area. Second, the recent publication of multiple major, practice-changing randomized trials in this area [20-23] highlight the clinical relevance of biologic principles such as altered fractionation, chemo sensitization, and molecular targeting. The head and neck is an ideal site for IMRT due to the complex geometry of this area and the severity of radiation-associated toxicity. Frequently, the distance between either gross tumor (gross tumor volume) or areas at high risk for microscopic disease (clinical target volume) and critical structures such as optic apparatus, inner ear, or salivary gland is no more than a few millimeters. Traditionally it has been extremely difficult or impossible to deliver a tumoricidal dose of radiation to the target volume while limiting the dose just a few millimeters away. Furthermore, the geometric relationships are complex. Targets are not centered in a 2D plane between critical structures; rather they are eccentric in a 3D volume, such as the ethmoid sinuses in relation to both optic nerves, retinas, optic chiasm, and brain.

Radiotherapy is used in the radical management of patients with head and neck cancer in many different clinical scenarios. It is used as a single agent or in combination with surgery, chemotherapy or molecularly targeted agents. Target structures include the primary, involved and uninvolved lymph nodes. Several critical structures limit tumor dose, including the parotid glands, spinal cord, optic apparatus and the swallowing apparatus. Late toxicity has focused on xerostomia and there is a well-documented relationship between the volume of parotid gland irradiated to 25e30 Gy and the long-term recovery of salivary function [24,25]. IMRT has primarily been used to reduce parotid gland irradiation, minimizing volumes receiving 26 Gy, although improved tumor coverage, reduced inhomogeneity and dose escalation have also been reported. Concerns over geographical miss and unexpected patterns of failure are now being reported [26,27]. The toxicity from head and neck radiotherapy is among the worst seen in the field. Radiation toxicities are defined as acute or late; acute toxicities are those seen during treatment and are usually self-limited, and late toxicities are those seen months to years after treatment and can be permanent. Acute toxicities related to radiation of the head and neck region include mucositis and its accompanying dysphagia and odynophagia, salivary changes including increased salivary viscosity, and dermatitis as severe as confluent moist desquamation. Late toxicities include xerostomia, sensorineural hearing loss, and the potentially catastrophic complication of vision loss. Loss of salivary function is by far the most common of these. Xerostomia negatively impacts quality of life, interfering with speech and swallowing and can contribute to the widely feared complication of mandibular osteoradionecrosis.

Reduced toxicity from IMRT may allow dose escalation or incorporation of concurrent systemic therapies, both of which might improve outcome [28]. Biological imaging may alter concepts in target delineation by identifying sites of increased clonogenic density or relative radio-resistance [29], to which IMRT could be used to deliver concomitan boosts [30].

IMRT for Prostate Cancer

An increasing number of men choose radiotherapy for the treatment of localized prostate cancer because of the perception that there is a lower risk of impotence and incontinence. Radiotherapy also avoids the need to take as much time off from work and is thus is less disruptive in terms of daily living. The downside of radiotherapy is a higher risk of rectal complications [31, 32]. Some men also are fearful that the results of radiotherapy may not be as good as radical prostatectomy. Recent data based on a large number of patients suggest that with higher doses of external beam radiation (72Gy) or brachytherapy, the likelihood of remaining disease-free at five years is comparable with radical prostatectomy [33]. .Although these data are from nonrandomized studies, they suggest that there are not likely to be large differences in the cancer control rates in the first five years after treatment. Furthermore,

there is no good evidence that there are more late failures after either form of radiotherapy than after prostatectomy [34-38]. 3D CRT first became available in the mid 1980s, and by the early 1990s reports from several institutions supported the notion that compared with conventional therapy, rectal toxicity was lower than expected despite higher doses. In a multicenter Phase I-II study, investigators from the Radiation Therapy Oncology Group (RTOG) demonstrated that radiation induced gastrointestinal complications appeared to be substantially lower than expected at various dose levels [39-41]**.** Similar preliminary results were reported from two small Phase III studies using cruder techniques [42-44]**.** However, the side effects reported in both of these trials appeared to be somewhat higher than in the larger multicenter RTOG trial. Furthermore, with longer follow-up, the incidence of late rectal bleeding was higher on the high dose arm in one of these studies, despite the use of 3D technology for the last part of treatment (or the "boost" dose)[44]**.** Other studies that have used 3D planning for the entire course of treatment, rather than just the last part of the treatment, had a lower incidence of gastrointestinal complications [39, 24]. The major lesson learned is that the risk of late complications may be increased if the 3D radiotherapy technique does not compensate for the additional dose. External beam radiation doses in excess of 70 Gy are required to yield the best results [33, 44-46], but the optimal dose remains to be determined. Although there are no prospective randomized clinical studies proving that IMRT reduces complications compared with 3D CRT, improvements in the radiation dose distribution with IMRT are easily shown [47, 48] [28-30]**.** Sequential dose escalation studies conducted at Memorial Sloan Kettering Cancer Center support the notion that the use of IMRT can reduce morbidity compared with 3D CRT [8]**.** In their analysis of over 772 patients who received doses in excess of 81 Gy (roughly 20% higher doses conventionally used in the past), with a median follow-up of 24 months, only 4.5% developed acute Grade 2 rectal toxicity, and none experienced acute Grade 3 or greater toxicity. Based in part on such favorable reports and with widespread availability, IMRT has become the standard therapy at many academic and private institutions. Despite the improved dose distribution associated with IMRT, the application of this technology to routine practice is limited by the increased potential for treatment errors that can result from organ movement and or daily errors in patient positioning [49]. The challenge of ever more accurately delivering radiotherapy precipitated the need for improved image-guided strategies spawning the concepts of image guided radiotherapy (IGRT) and 4D CRT. The fourth dimension in this setting refers to the impact of time on the position and/or shape of the target volume.

IMRT for breast Cancer

Breast cancer is the most common form of nondermatologic cancer in women [50,51]. As more women choose breast conservation therapy (BCT), breast radiation therapy is a large component of a radiation oncology practice. The advances in radiation technology have made standard radiotherapy much more precise and discriminating. Until recently, the total time and dose of standard radiation had not significantly changed in over 20 years with the exception of a possible 10 to 16 Gy electron boost to the surgical cavity [52,53]. Nagging questions persisted, driving current clinical research into a new era, particularly for women with early-stage breast cancer who are candidates for BCT. The key questions are: can we shorten the duration of standard breast irradiation, can we treat a portion of the breast instead of the whole, and can we select women who can avoid radiotherapy altogether? The issue of avoiding radiotherapy in BCT has been explored in the past and recently revisited in two current articles published in the New England Journal of Medicine [54,55]. Before these articles, the National Surgical Adjuvant Breast and Bowel Project-21 trial randomized approximately 1,000 women of all ages with invasive tumors less or equal to 1 cm treated with lumpectomy and axillary node dissection to radiotherapy and tamoxifen, radiotherapy and placebo, or tamoxifen alone. The cumulative incidence of ipsilateral breast tumor recurrence was 2.8%, 9.3%, and 16.5%,[56] respectively. Distant metastases and overall survival were the same for all groups. This study did not select patients based on age, estrogen receptor status, or grade. The first of the two New England Journal articles, from the Princess Margaret Hospital, randomized 769 women aged 50 years or older with node negative invasive breast cancer 5 cm or less to breast irradiation and tamoxifen versus tamoxifen alone. Again, there was no difference in the rates of relapse or overall survival; however, local recurrence in the breast and axilla were significantly reduced in the radiotherapy arm including a subgroup analysis of those with tumors less than 2 cm.86 The only study where the authors concluded that it may be reasonable to omit breast irradiation and treat with tamoxifen alone randomized 636 women who were 70 years or older with estrogen receptor-positive, early-stage breast cancer (node negative and 2 cm) to breast irradiation plus tamoxifen or tamoxifen alone and at five years median follow-up showed a rate of local or regional recurrence rate of 1% and 4%, respectively, with no significant difference in the rates of mastectomy, distant metastases, and overall survival[54]. The main criticism of the study is that longer follow-up is needed. The eligibility for BCT is assessed by clinical examination, imaging studies, pathology, individual preference, and expected cosmetic outcome (best with small tumor to large breast size). Still today, women who qualify for breast preservation may opt for a mastectomy to avoid the 5 to 6.5 weeks of Monday through Friday radiotherapy. Radiotherapy is often at the tail end of surgery and months of chemotherapy, presenting a final test of endurance and a new source of anxiety. Distance from the radiation facility plays a factor in the decision

making process, as the inconvenience of daily transportation and the time commitment must be integrated into an already busy schedule [57].

Two current aspects of breast irradiation are hot topics and have provided the momentum for ongoing and future investigations. The first of these is the role of advanced treatment techniques in producing conformal homogeneous dose throughout the breast while attempting to protect the critical structures such as the ribs, lung, and heart. The second is the provocative topic of shortening the course of radiotherapy. The current climate for addressing accelerated treatment is often mixed with the concept of only treating a portion of the breast, or partial breast irradiation, instead of the whole breast. In part, this is because the design of the popular devices used to deliver the radiation can only treat the part of the breast at highest risk of recurrence the surgical cavity and the adjacent tissue. Candidates for accelerated irradiation are low-risk, early-stage patients for which a variety of definitions apply.

IMRT for Lung Cancer

Radiotherapy is used for many patients with both small cell and non-small cell lung cancer, but long-term outcomes remain relatively poor. There are many critical normal structures in close proximity to targets (including the oesophagus, lung, spinal cord and heart if mediastinal nodes are irradiated) and there is evidence for a dose volume relationship for late pulmonary toxicity [58]. Internal organ motion is of considerable importance and consideration of respiratory motion is critical during target volume delineation, margin application and treatment delivery.

IMRT for Gynecological cancer

IMRT is receiving increasing attention in the treatment of these sites because of established dosimetric advantages of normal tissue sparing. In fact it can benefit over conformal/3D technique in any situation/site where Teletherapy is being planned. Example Pelvic/Extended Pelvic or Pelvic-Inguinal fields. The controversial role of IMRT includes its ability to provide dose escalation in situations where ICBT is not possible or suitable. [18-21]. A few special clinical settings where IMRT may show some clinical benefit over 3D techniques include management of recurrent disease in previously irradiated patients. It may even have a limited role for palliation in situations where the target is very near to or wraps around normal tissue, e.g. retroperitoneal lesions and paraspinal tumor/nodes. Of course any treatment in the palliative setting should be limited to a potential extended survival and a risk for anticipated late effects. An interesting concept being evaluated in this set up includes dose escalation for sustained palliation, for example patients with localized bone metastasis or plasmacytomas. Another theoretical concept is reducing the toxicity of prophylactic cranial irradiation. IMRT could selectively spare the outer cortex and hippocampus (cognitive function) when considering prophylactic RT to the whole brain as a component of CNS directed therapy in Leukemia protocols. Although the entire brain is currently irradiated most metastasis occurs in the watershed areas and grey white junctions [63]. IMRT in the set up of re-irradiation provides the ideal provision of extending the maximal feasible dose while sparing normal tissue toxicity. The promising results of a few re-irradiation series (using 3D conformal RT) was mainly compromised by unacceptable toxicity and risk of reducing quality of life [64]. However the current clinical scenario does not find the time and cost function favorable for using IMRT in these situations in routine clinical practice.

IMRT Vs. older technique

One of the biggest challenges of treating NPC using conventional techniques is to prescribe a tumoricidal dose to gross disease without causing clinically important toxicity in normal structures. Two-dimensional RT (2D-RT), typically with opposed lateral portals, did not permit equivalent sparing of normal structures without under-treating gross disease. Common toxicities with this technique, particularly with concurrent chemotherapy, included: xerostomia, occurring in over 90 % of patients and 70 % have reported moderate or severe symptoms [65,66], mucositis, where significant mucositis have been reported from 33 to 64 % of patients[67-69] , and dysphagia, where the most common dysfunction was pharyngeal retention ranging from 77 to 93.5 %[70-72] . Two-year locoregional recurrence rates ranged from 13 to 26.6 % and 5-year survival rates ranged from 43.5 to 70.6 %[73]. Three dimensional conformal RT (3D-RT) was an improvement over 2D-RT, but still had difficulty covering the target when it was close to critical structures such as the brainstem. The benefit of IMRT over 2D-RT or 3D-RT is that it can improve coverage to disease while reducing dose to adjacent organs.

Dosimetric advantage of IMRT

Several institutions have shown an unquestionable dosimetric benefit of IMRT for NPC over conventional techniques [74, 16]. Hunt et al. showed that compared to 3D-RT, IMRT lowered doses to the spinal cord, mandible, and temporal lobes while increasing coverage to the retropharynx, skull base, and nodal regions [74]. Xia et al. compared IMRT, 3DRT, and 2D-RT plans for locally advanced NPC [16]. They found that IMRT was able to achieve the same dose coverage to the target volume, while reducing dose to the parotid gland, optic chiasm, and brainstem. An additional dosimetric advantage of IMRT is simultaneous delivery of different doses during every fraction of treatment. This can allow areas of subclinical disease to receive adequate lower doses compared to gross disease where doses can be substantially higher. This technique has been referred to

in the literature by a variety of terms including simultaneous integrated boost, simultaneous modulated accelerated RT, or dose painting [17, 75-76]

FUTURE PERSPECTIVE

1. Need more clinical data on outcomes.
2. Establish and refine appropriate patient selection.
3. Improvement in treatment planning and delivery.
4. Need cost analysis.

Much of the work on IMRT physics has been done for the currently available IMRT systems. However, clinical data remain scarce. Before IMRT can be widely implemented and accepted as a standard of care, we should have more comprehensive clinical data on the outcomes of IMRT treatment to substantiate its superiority and advantages over conventional modes of radiotherapy. These should include outcome studies addressing both tumor control and quality of life. The use of IMRT is hoped to improve the tumor control by permitting a dose escalation without increasing the risk of injury. However, this potential gain could be jeopardized by increased marginal miss due to inadequate coverage and, thus increased local or regional recurrence. We also need quality of life data to demonstrate that IMRT indeed can reduce the late effects and risk of complications from radiation treatment. We should further define patient selection criteria and improve treatment efficiency for IMRT. Last but not least, a comprehensive cost analysis of IMRT should be performed to better improve cost effectiveness of the new modality.

CONCLUSION

IMRT is a promising new technology that provides an improved radiation delivery technique. It is hoped that IMRT will improve local control or cure and/or reduce the risk of severe late effects and complications of radiotherapy. However, its true clinical benefits are yet to be proven. Currently, available IMRT remains costly and inefficient. Greater cautions and judgments are needed in selecting patients for IMRT.

In summary, there have been several exciting technical advances in radiation therapy, including IMRT, IGRT, and 4D RT, and several investigational new devices in the treatment of breast cancer. These modalities are more commonly finding their way into clinical practice, and early data are emerging on their effectiveness. Data have recently become available confirming the advantages to concurrent chemotherapy and targeted therapies such as cetuximab with concurrent radiation in the head and neck, adding to data about the role of combined modality therapy in other sites, such as lung and colorectal cancers, gained over the last decade. We are optimistic that the next decade is likely to yield more advances regarding the role of radiotherapy in an increasingly multidisciplinary oncology environment.

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