Intensity modulated radiotherapy (IMRT) the white, black and grey: a clinical perspective

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ABSTRACT

The radiotherapy community has in the past few decades witnessed dramatic shift in the treatment modalities from conventional 2-D radiotherapy to the now widely practiced 3-DCRT, IMRT and evolving IGRT. IMRT has generated so much interest because of its unique dosimetric modulation to concentrate doses to the targets of interests while also being able to relatively spare neighboring normal tissue. However IMRT is not the all in one solution for radiotherapeutic management of solid malignancies. The current enthusiasm in IMRT most be tempered with an understanding of the complexities of IMRT planning, treatment delivery, quality assurance, monitoring and clinical limitations. The widespread implementation of this technological innovation may have been a bit premature considering that clinical information regarding the same is still being generated. This article tries to give an overview of the potential advantages/disadvantages of IMRT in the clinical set up and the few controversies (Grey Zone) that are still being resolved. There is evidence to indicate that indiscriminately used IMRT may even harm the patient or have an inferior therapeutic index to 3DCRT. This and other pertinent issues will be covered by the authors in this short review of IMRT in clinical practice.

KEY WORDS: intensity modulated radiotherapy, conformal radiotherapy, dose optimization, advances in radiotherapy

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INTRODUCTION

Current status of IMRT

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 its 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].

Prostate cancer

This site to date provides the largest clinical experience with IMRT. There is comparative data to show benefit over 3DCRT in several clinical issues [10].

Zelefsky et al have reported the largest clinical experience with IMRT used for patients with localised carcinoma prostate. They have also done a comparative study with 61 patients undergoing 3DCRT. Normal tissue toxicity was considerably reduced. The 2 year acturial risk for grade 2 bleeding was 2% for IMRT vs 10% for 3DCRT(p<0.001). An updated report by Zelefsky and colleagues evaluating 772 patients undergoing IMRT showed a very promising 3 year acturial biochemical control rate for favorable (92%), intermediate (86%) and unfavourable risk patients (81%) [11–12].

The SIB technique (Simultaneous Integrated Boost) with hypofractionated radiotherapy with greater than 2 Gy/fraction is currently being evaluated for its potential to improve upon their results.

Head and Neck cancer

The most convincing data of the superior therapeutic gain achievable with IMRT are

from tumors close to base of skull such as Nasopharynx and Sinonasal cancers in which a higher rate of local control and lower incidence of complications have been documented [13, 14]. In terms of clinical outcome reports from University of California Sanfransisco and Memorial Sloan Kettering Cancer Center (MSKCC) show excellent locoregional control, greater than 90% and substantially lower rates of Xerostomia [15–16]. Additional potential functional gains from IMRT compared with conventional RT include improved swallowing and speech , thus translating into improvements in broad aspects of Quality of life.

Clinical data on other Head and Neck sites are still quite limited on account of small numbers, heterogenous tumor sites and relatively short follow up. Although providing the preferred treatment for most Head and Neck sites on account of less anticipated motion and proximity to critical normal tissue; there are situations where it may be less than optimal. To cite a few clinical examples, Early Vocal cord carcinoma with anterior comissure involvement may risk having a geographical miss on account of the dose characteristics of low energy photons. In this situation conventional radiotherapy may provide an equivalent therapeutic index, as normal tissue toxicity is not unduly compromised with the recommended portals used for this stage. A well lateralized T1 oral cavity lesion can be efficiently treated with 3DCRT with a comparatively lower dose if any to opposite parotid. IMRT in such a situation would contribute atleast a marginal low dose to the opposite side of the face and neck (increased integral dose and low dose volume).

The 3DCRT technique would have equivalent clinical results with the advantage of being more time and cost effective.

Carcinoma Breast
Theoretically and practically, IMRT at this site does provide some clinical benefit. It improves dose homogeneity within breast tissue in comparison to conventional/conformal treatment.

When IMC/Axillary nodal regions are a part of the clinical target volume, it can provide a comparatively better sparing of ipsilat-

eral lung/cardiac volumes. This may be even more significant pertaining to left sided tumors. IMRT studies with treatment of intact breast has shown lower incidences of acute and chronic skin reactions compared to retrospective series. However several unsolved issues prevent it from being the standard of care. Specific measures may be required to counteract the effect of breathing motion .Respiratory gating is still not an accessible option for majority of centers with IMRT facilities. The improvement in dose homogeneity within the target volume and restriction of high dose to normal tissue , comes at the cost of subjecting contralateral lung to lower doses of RT not normally irradiated. We are now observing an increasing incidence in younger patients who may have many expected years of survival to be accounted for by the increased incidence of developing a secondary cancer [17]. With current limited data on the long term risks of 2nd malignancy with IMRT it may be required to limit IMRT to the subset of patients most likely to achieve a therapeutic gain especially considering the fact that 3D radiotherapy at this site provides acceptable dose distribution and limited normal tissue toxicity.

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. Eg. Pelvic/Extended Pelvic or Pelvic-Inguinal fields. The controversialrole of IMRT include its ability to provide dose escalation in situations whereICBT 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, Eg. retroperitoneal lesions and paraspinal tumor/nodes. Of course any treatement 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 include dose escalation for sus-

tained 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 [22].

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 [23].

However the current clinical scenario does not find the time and cost function favorable for using IMRT in these situation in routine clinical practice.

I Which Patients will benefit from IMRT?
This is a grey zone with many unanswered questions. Long term clinical results of IMRT have only began to emerge. It is still to early to recommend IMRT as the standard of care. In terms of curative management of malignancy, the most important caveat of IMRT is its potential for dose escalation. Significant clinical results are available to suggest that dose escalation with IMRT dose translate to improved local control in carcinoma nasopharynx and carcinoma prostate. The escalation of dose by simultaneous integrated boost (SIB) to a tumor dose of 76 gray for treatment of locally advanced nasopharyngeal carcinoma has shown good short term outcomes [24]. Local control and overall survival reported are 96% and 92% which is significantly higher than that anticipated for similarly treated disease with 2D/3D technology. The excellent local control rates may to a certain degree be attributed to the better coverage made possible with IMRT, especially for retropharyngeal, base of skull and medial aspects of nodal volume [25]. There is positive evidence to show that increasing dose for prostate radiotherapy from 70 to 78 Gy in intermediate and high risk prostate cancer would translate to better local

control [26]. In addition dose's of 81 Gy have resulted in a 7% positive biopsy rate compared to 45% with lower doses.

The following table may suggest a few limitations of IMRT in the clinical set up. Patients who will definitely benefit from IMRT.

II Grey Zone
Patients whose cancers may have equivalent or better result with 3DCRT. E,g: Brain tumors, localized early oral/oropharyngeal cancer requiring ipsilateral treatment.

III Patients who may be harmed by IMRT
1. Pediatric malignancies with good anticipated long term survival rates. The nearly 2 times increased potential for second malignancies cannot be ignored.

2. Adult tumors in younger age group with long term anticipated survival rate Eg Carcinoma breast, Lymphoma.

3. Thoracic lesions when gating and other respiratory movement control methods are not being integrated. In this scenario there is a significant risk of geographical miss. The type of margins required to contour, the anticipated movements negate the benefit of dose conformation.

Considering the high cost of treatment, longer and more intensive physician, physicist, technologist and machine time and effort involved in IMRT planning and delivery it is critical that patients best benefited should be identified and those who are not be realistically offered alternative treatments.

The Role of Imaging
The need for accurate determination of larger volume and geometry of the organs at risk (OAR) in IMRT cannot be over emphasized. The dosimetric advantages of IMRT can be clinically realized only if the anatomical boundaries are precise. Early accurate delineation of target and contouring of OAR can be achieved with CT imaging in most situation. A generalized overview of the role of image fusion is given in table 2.

Will functioning imaging make a difference?
Considerable data is available for IMRT in Head and Neck sites to suggest 14–20% of re-

Table 1. A few limitations of IMRT in the clinical set up

Sl no	Comment	Application
1	Clinical evidence of dose dependent response.	Nasopharynx Ca Prostate
2	Conformal dose distribution required, not achieved with 2D CRT	Paraspinal Lesion Concave targets.
3	Avoidance of critical structure and les toxicity desired	Gynecological malignancies Ca Rectum.

Table 2. A generalized overview of the role of image fusion

Imaging modality for integration in IMRT planning	Clinical role	Comment/limitation
Computed Tomography	Integration of additional data to that of CT simulation	Pre-treatment size specification when tumor shrinkage has occurred with neoadjuvant CT.
MRI	Superior contrast resolution for soft tissue. MRI in any arbitrary plane allows for cross reference of tumor dimension. Studies of MRI integration in planning of brain tumor show significant reduction in interobserver differences.	MRI images may be subject to geometric distortion due to patient and respiratory movement. (Long imaging time).Bone is imaged negatively and may not be distinguished from air space. Image fusion may not be accurate and occasionally not feasible if comparable imaging set up is not reproduced.
Functrioanl Imaging [27]	Provides information on activities and functional map of the brain.	Better delineation of the brain, tumors and functional areas.
PET: [18] FDG [28, 29, 30]	Provides a biological target volume (BTV). This allows for CTV identification and dose restriction/escalation depending on the additional information conveyed.	FDG 18 PET may identify 1) More extensive loco regional disease expanding CTV / PTV coverage. 2) Identify smaller volume of GTV/excluding doubtful lymphadenopathy, benign tissue example atelectasis and necrosis thus restricting tumor and planning target volume

currences occur as marginal with same sites showing as high as 19% outfield recurrence. FDG 18 PET could potentially prevent such planning errors.

However contrary to expanding volumes analysis of 25 head and neck cases for IMRT by Mezen E, Basinouni et al [29] have shown GTV PET was significantly smaller than GTV-CT (p-0.0022).

Paulino et al [30] showed similar data in 75% of patients analyzed.
CTV CT/CTV PET – 1.7 to 2 (32.3% of cases)
GTV CT/GTV PET – 2.1 to 3 (22.2 % of cases)

This would indicate that the shrinkage of fields would have probably permitted a plan better optimized for normal tissue sparing. Considering both the aforementioned factors FDG 18 PET would be a very useful planning tool for designing a more optimized plan. Another avenue of current attention is the use of integrating image modalities for adaptive radiotherapy. Brahme et al [31] had suggested that PET-CT could be used for adaptive radiotherapy by measuring the mean dose delivery during the early part of the treatment to review the treatment plan. PET-CT for dose escalation for metabolically active sites is currently speculative but does hold promise.

Defining the target Volume:
Tight margins Vs Geographical miss.

Proper contouring of targets and normal tissue is critical to the usefulness of any IMRT plan. Physician induced variability in contouring can exist even in the same department. Over statement/under statement of treatment margins and volumes cloud lead to geographical miss and compromised cure. On the other hand over generous margins may lead to poor normal tissue sparing and reduced benefits.

A study of Phillippe Giraud, Sabine Elles, Sylvie Felfre et al had analyzed 10 patients of non-small cell lung cancer. The study compared interobserver error

1. Between Radiologists & Radiation Oncologists.

2. Senior Vs Junior radiation Oncologist

It was observed that mean GTV volume was 133.6 cm³ vs 97.9 cm³. There was significant contouring differences between the two (p=0.1). Analysis of data from multiple centers show a much more significant difference than that observed from interdepartmental variations.

In comparison of Junior radiation Oncologist Vs Senior Radiation Oncologist, it was observed that junior oncologist delineated smaller volumes than senior radiation oncologist, however the difference was not significant.

A few of the variations in both set-up could have to a small degree be attributed to an inferior knowledge of radiological anatomy than to difficulties of visualization specific to the patient, for example confusion between hilar structures or mediastinal fat, tumor tissue Vs artifacts in the lung.

The two most reliable methods to reduce interobserver error (details previously addressed) is integrated image fusion having structured departmental protocols.

As far as possible departments should prepare guidelines with respect to identification of tumor volume/extent for example image fusion or collaborate to have a consultant radiologist on call. It would be recommended to strictly adhere to the broad outline of ICRU 50/ICRU 60 methodology for defining target volumes [34].

Preparing site wise protocols may aid in avoiding interobserver variation and preparing a standard radiotherapy treatment plan.

Some of the pitfalls encountered in IMRT contouring include those mentioned in table 3.

IMRT contouring is admittedly time consuming with a minimum of 1–3 hrs of physicist time involved. The current generation of auto-segmenatation tools have their limitations and should not be used indiscriminately. An example of some of the errors involved includes contouring of irregular volumes. Margin for structure when auto-segmented may not be uniform in all cuts. There may be a 5 mm to 15 mm variation from the margin specified in the command. Auto segmentation of spinal cord often results in inclusion of the entire spinal canal. This prevents giving a realistic margin when adding organ at risk margins.

So although these tools help to reduce planning time, they should be implemented with caution and be substantiated with cut by cut review of contoured images of targets, margins and normal tissue.

Choosing an ideal margin CTV – PTV

The CTV – PTV margin aims to account for patient setup uncertainty and internal organ motion. Regions with minimal anticipated internal organ motion and good immobilization like brain/head and neck sites, the margins can afford to be narrow (3–5 mm). Areas with more anticipated internal organ motion like genitourinary and gastrointestinal sites require more generous 1–2 cm margins. But do these guidelines fit every situation? Probably not. Internal organ motion can vary from patient to patient (anxiety may alter respiratory rhythm and bowel habits determine GI motility). Set up uncertainties may also differ depending on the immobilization system or set up direction/mounting used at a particu-

Table 3. Some of the pitfalls encountered in IMRT contouring include

Tumor/Target Volume	Recommendation	Comments
GTV	Gross evaluable extent of tumor aided by integrated image fusion.	Considerable interobserver variation.
CTV1/CTV 2	Margins for these volume are guided by clinical risk of microscopic disease as indicated by the biology and stage of the tumor. Considerable interpretative errors can occur in terms of treatment decision as well as identification of high risk/low risk volume.	Specific Guidelines for individual sites often do not exist. The few guidelines that are available often will have to be tailored to the clinical situation. This makes most plans difficult to compare for clinical data.

lar institute. Taking these uncertainties into consideration, there is a need to create an institutional protocol for CTV – PTV margin for various sites. An institution population based formulation can be considered to provide the most ideal treatment margin. Marcel Van Herk, Peter Remeijer et al have shown from a population based analysis of patients in their institute that a correct target dosage can be reasonably achieved by computing the ideal margin from analysis of systemic and random errors. Large execution errors (random) lead to CTV under dosage for a large number of patients while large preparation errors (systemic) lead to a large under dosage to some patients. To ensure a minimum dose of 95% to the CTV of 95% of patients a margin between CTV and PTV is required of 2.5 times the total standard deviation of preparation (systematic) errors plus 1.64 times the total execution (random errors) combined with the penumbra width minus 1.64 times the SD describing the penumbra width. Because the margins excludes rotational errors it might be considered as the lower limits for safe radiotherapy.

The total PTV margin can be represented as $M_{PTV} = \alpha \sum + \delta \rho \beta$ [32, 37]

M PTV – ptv margin

β – 95 % of cases is 1.64

δ – total SD of all treatment execution (random) variations, (organ motion δ m and set up error δ s combined with the penumbra $\delta \rho$.

α – the specific value of α for 90% confidence in 3DCRT is 2.5.

Thus the mathematical formulation can anticipate the optimal CTV – PTV margin that can be instituted as a departmental protocol for that particular site. The alternative would be to customize the treatment after evaluating patient related set up errors during the first week of treatment. The downside of this is replanning may be required and the patient might miss the optimal treatment prior to finalizing the margin.

Generation of adequate margins for normal organs at risk may be required to accommodate for sharp dose gradient in IMRT, especially considering the high radical dose prescribed [33]. Current work is focused on assessing normal tissue organ motion on serial CT scans and anticipating the internal organ motion components.

IMRT fractionation schedules: Pros & Cons
What fractionation to choose?

The fractionation designs mainly incorporated into clinical practice include IMRT boost protocols and SIB (Simultaneous integrated boost) and its variations Example of IMRT boost plans include:

a) Initial phase – 3DCRT + IMRT boost

b) Initial phase IMRT + IMRT boost (plan -2)

The theoretic disadvantage of these boost protocols is that a large part of the dose delivered in phase I, uses larger fields and therefore the dose conformation achieved may not provide additional benefit to normal tissue sparing. For example in considering Head and Neck treatment plans.

– Objective of keeping spinal cord below 45 Gy is often not met.

– Sub clinical disease gets more than the planned dose of 50–54Gy.

– Although dose to parotids will be comparatively less than conventional plans; desired dose tolerance limits are often exceeded.

– This would dilute the anticipated benefit of IMRT.

SIB and its variants

SIB or Simultaneous Integrated Boost may now be considered the strategy of choice for IMRT for most centers. This fractionation scheme aims to deliver several different dose levels to tumor (higher) and normal tissues (lower) in single treatment session. That is to say that in each fraction dose to tumor, elective CTV and normal tissues will be different. SIB may be designed in 2 types of formats. In the more commonly used one the target is planned to get conventional fractionation while the simultaneously irradiated CTV1 and CTV2 will get comparatively lower dose per fraction. Normal tissue at risk will be receiving an even lower dose/fraction. Disadvantage of this plan is the uncertain radiobiological benefit of delivering less than 1.8 Gy per fraction to subclincal disease.

The second strategy would involve delivering greater than 2 Gy/Fraction dose to the primary (hypo fractionation) target volume maintaining normal tissue at conventional doses. Although providing the benefit of biological dose escalation, this plan has a risk of unanticipated complication. The hypofraction-

ation although beneficial toward tumor control carries a risk to the embedded normal tissue. The choice of SIB should therefore take into consideration the clinical outcome data.

Several recent studies [35–39] have suggested that alpha/beta values for prostate is comparatively low with the probability of benefiting from hypo fractionation (SIB scheme 2). Considering the above; in principle IMRT provides an easier more efficient form of IMRT delivery with benefit of single plan, shorter duration of treatment and avoidance of errors associated with field matching and dosimtereic uncertainties of combining with electrons.

Plan evaluation:
Dose distributions: To be or not to be.

IMRT plan evaluation differs from 3D plan evaluation in several clinical aspects that should be evident to physician at the time of evaluation. Notable is the trade off between conformity and dose heterogeneity. If the priority is conformity one may have to accept considerable dose heterogeneity. An other factor that may contribute towards the latter would be increased concavity of target. A slice by slice evaluation of dose distribution in comparative 3DCRT and IMRT plans often reveal a larger number of hotspots within the target often greater than 110%. Unexplained hotspots may also be thrown on normal tissue contoured as well as other non contoured area within the fields. Fine tuning of the treatment plan would be more efficient and faster if there is clear cut guidance from the physician as to what goals have more importance and where and how doses can be permissibly compromised.

Is there a better alternative?

Treatment delivery with IMRT is not without its drawbacks. The treating physician should be realistic about the additional 1.5 to 2 times dedicated effort and time required for treatment planning, evaluation, delivery and quality assurance compared to conventional and 3D treatment plans. As mentioned previously large volumes are being exposed to low doses and with additional risk of head leakage, neutron production and scatter with its attendant greater risk of second malignancies [40–43].

Considering the above IMRT should be selectively instituted in situations with a more than marginal benefit either in terms of dose parameter achievable or normal tissue sparing and preferably with both parameters benefited. Whenever the target is well localized or lateralized, it may be preferable to consider a 3D plan as an alterative during plan evaluation. For example a very early stage lateralized oral cavity lesion may have better normal tissue sparing (contralateral parotid receiving none or negligible dose) and total tissue irradiated less with comparative dose goals achieved to an IMRT plan. In such situations it may be advisable to go for the benefit of a 3D CRT plan.

Weighing the cost benefit

This has to be viewed from 2 angles. From a patients' point of view, the cost of IMRT in most cases is 70–75% more expensive than 3DCRT. With limited long term data available the physician is handicapped to provide positive evidence of benefit and as mentioned previously it may not be necessary to treat all patients with IMRT. In addition to which ethical issues would arise considering machine time dedicated to IMRT delivery. Would we be delaying treatment of patients who may be benefited by earlier 3D/2D plans?

What does the future hold?

At the foremost of current interest is the possibility of biological dose painting, integrated fusion, functional imaging, targeting metabolic activity, hypoxia, angiogenesis etc.

Incorporation of radiobiological indices may allow for a more realistic choice regarding dose fractionation. Various modes of IGRT are being more popularly used with considerations to further reduce the risk of set-up and internal organ movement errors. The evolving technology of 4DCRT, respiratory gated target motion compensation and immobilization of targets by breathing control during treatment facilitate safe delivery of a highly conformal escalated dose to the target minimizing margins required thus also further benefiting normal tissue sparing.

CONCLUSION

IMRT has shown clear cut dosimetric benefits over conventional 2D/3DCRT treatment

techniques both in terms of tumor dose conformity and normal tissue sparing. Clinical data although still immature, is emerging to suggest the enhanced therapeutic ratio and possible survival advantage of this modality of treatment. This benefit has been confirmed in some sites with clear cut dose response relationship for example Nasopharynx and Prostate. However IMRT cannot be considered a universal solution and has a long way to go before becoming the standard of care. The prohibitive cost of this technology will still make it unacceptable to majority of cancer population that may require it. However it is the current baseline over which research and development work is being conducted. Exciting progress is being made in the areas of biological imaging and targeted dose delivery. And it may not be far to look forward to their incorporation into clinical practice.

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