



# Modern Radiation Oncology: From IMRT to Particle Therapy—Present Status and the Days to Come

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## Abstract

There has been tremendous technological development in the field of radiation oncology, mainly during the last few decades. Parallel advancements in imaging and accelerator technologies have contributed significantly to the same. Present-day radiation therapy is aimed at precision, in terms of physical accuracy of both its planning and delivery. This has been made possible by improvements in defining the target (use of various radiological and functional imaging modalities), advanced radiotherapy planning methods (intensity-modulated radiation therapy and recent emergence of particle therapy), and robust verification techniques (image-guided radiation therapy). These developments have enabled delivery of adequate tumoricidal doses conforming to the target, thereby improving disease control with reduced normal tissue toxicity in a wide range of malignancies. Elucidation of molecular pathways determining radioresistance or systemic effects of radiotherapy and strategies for therapeutic manipulation of the same are also being explored. Overall, we look forward to ensuring basic radiotherapy access to all patients, and precision radiation therapy to appropriate candidates (triaged by disease anatomy or biology and associated cost-effectiveness).

## Keywords

- evolution
- IMRT
- radiation oncology

## Introduction

In the past century, the field of radiation oncology has witnessed remarkable leaps in terms of techniques related to planning as well as delivery of treatment. Starting from orthovoltage radiation in the early 1900s to the highly efficacious heavy ions in the present era, from surface marking-based planning to the complex intensity modulated planning methods, the evolution has resulted in significant improvement in therapeutic ratio. This has enabled increased use of radiotherapy (RT) in curative setting in a

diverse group of tumors, leading to a paradigm shift in management in favor of organ preserving definitive RT in some of them.<sup>1</sup> Herein, we briefly review the evolutionary steps and present status of modern external beam RT and the future perspectives.

Introduction of three-dimensional (3D) volumetric imaging in 1970s had brought revolutionary changes in the way RT is planned. There was improved accuracy in defining target (cross-sectional delineation of irregular tumor volumes) and planning irradiation portals (advent of treatment planning systems that use volumetric images and dose

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calculation algorithms). Parallel improvements in linear accelerator (LINAC) hardware (e.g., multileaf collimators) have enabled conformal delivery of irradiation. Taken together, the transition from conventional to 3D conformal radiotherapy (3D-CRT) was a significant leap that translated to improved clinical outcomes in a variety of cancers.<sup>2,3</sup>

Further efforts soon followed, to refine the conformity of RT dose to correspond to complex and irregular shape of targets. Initially, attenuating blocks or primitive collimators were used for intensity modulation of a beam to achieve the same.<sup>4</sup> In the 1980s, Brahme et al postulated the concept of modern intensity modulated radiation therapy (IMRT), that is, achievement of a predefined conformal dose distribution, by rotation of symmetrically nonuniform intensity profile.<sup>5</sup> However, the concepts were technically made possible only in the 1990s with the advent of new hardware and algorithms.<sup>6</sup> This has brought in spurts of many other developments in the field as summarized below.

## Improvements in Defining Target

With even the most complex and advanced treatment planning system or LINAC, it is the mandate of the oncologist to accurately define the area to be treated. In fact, incorrect delineation is one of the commonest causes of geometrical miss of tumors.<sup>7</sup> Advanced multimodality imaging modalities, used routinely for staging of cancers, are commonly utilized today in RT planning. High-resolution magnetic resonance imaging (MRI), positron emission tomography (PET) using various tracers for specific purposes, dynamic contrast-enhanced computed tomography (CT), functional MRI, etc., are to name a few.

Generation of algorithms to enable coregistration or fusion (rigid or deformable) of simulation CT with these imaging modalities helps in accurate delineation of disease in many tumors. Specifically, fusion with MRI is helpful in delineating tumor bed in breast cancer as well as in soft tissue tumors of abdomen and pelvis<sup>8</sup>; whereas molecular imaging is helpful in lymphoma, tumors of head and neck, lung, esophagus, and to some extent in soft tissue sarcomas.<sup>9</sup>

The advanced imaging armamentarium assists us in defining not just the morphological extent of tumor but also to localize the radioresistant areas inside it, which can be treated to a relatively higher dose (*dose painting*).<sup>10</sup> There is an evolving concept of *Biological Target Volume* that is defined taking the functional imaging particulars into consideration. Defining hypoxic areas inside the tumor using diffusion weighted sequence of MR or F-Miso-PET is an example, with promising outcomes. Similarly, PET-based boost of viable tumors is under trial with awaited clinical outcomes in lung cancer. Additionally, use of “imaging biomarkers” from high-resolution perfusion images or dual-energy CT may pave a path toward personalized RT.

To minimize the uncertainties associated with coregistration, MR simulators that allow generation of synthetic CT images (which can be used by dose calculation algorithms) are a notable recent development.

There has also been implementation of various image segmentation techniques, based on atlas or deep learning models to define organs at risk (OARs) or targets.

## Improvements in Planning (IMRT)

IMRT is an advanced RT planning process in which the desired dosage to the target as well as the dose constraints to the adjacent OARs are predefined and the required beam intensities to deliver the same are inversely calculated by iterative calculations and various algorithms. Many optimization methods, to achieve the same, have evolved and are in use in recent times, details of which are beyond the scope of this review. Volumetric-modulated arc therapy is a refined recent way of IMRT with variation in dose rate, gantry rotation speed, and treatment aperture shapes. This has the advantage of rapidity in treatment delivery with lesser monitor units compared to fixed-field IMRT. The ability to conform to small fields has enabled highly conformal hypofractionated (often to a lethal dose) IMRT techniques namely Stereotactic radiosurgery and stereotactic body radiotherapy (SBRT) that have gained clinical usage across a wide spectrum of disease and sites.

Benefits achieved with IMRT include the following:

a) *Improved local control*: This is attributed to the ability of dose escalation and simultaneous integrated boost, both of which have biological impact on tumor cells. The benefits are clinically seen in various sites that are usually surrounded by critical OAR, namely skull base tumors,<sup>11</sup> paranasal sinus tumors,<sup>12</sup> nasopharyngeal tumors,<sup>13,14</sup> prostate cancer,<sup>15</sup> and parameningeal pediatric rhabdomyosarcoma.<sup>16</sup> SBRT has shown excellent clinical outcomes in early stage nonsmall cell lung cancers,<sup>17</sup> certain intracranial tumors,<sup>18</sup> nonmetastatic renal cell carcinoma,<sup>19</sup> oligometastatic disease in different sites (Stereotactic Ablative Body Radiotherapy [SABR]-COMET trial),<sup>20</sup> and pancreatic cancers.<sup>21</sup>

b) *Reduction in treatment-induced toxicities while maintaining excellent control rates*: Benefits of RT seen with older techniques were offset by the toxicities having impact on survival and quality of life. Increased cardiac mortality in patients receiving adjuvant radiation for breast cancers, dysphagia aspiration-related deaths in treated head and neck squamous carcinoma (HNSCC) patients are classic examples of the same. Xerostomia was a very common and troubling symptom in a major proportion of HNSCC patients. Use of IMRT has resulted in significant reduction in xerostomia and dysphagia-aspiration-syndrome in HNSCC.<sup>22,23</sup> Similarly, in patients receiving RT to mediastinum or breast, the risk of cardiac morbidity and mortality can be significantly curtailed.<sup>24,25</sup> Hippocampal sparing whole brain RT in patients of brain metastasis also results in better cognitive function, as shown in patients with lung cancer (NRG Oncology CC-001).<sup>26</sup> Reduced acute and late toxicities in postoperative irradiation of cervical cancers have established IMRT as the preferred treatment technique in these patients.<sup>27</sup>

The potential concerns with IMRT include higher possibility of second malignancy due to a wider area of low dose bath, and possibility of geometrical miss of target (and the consequent risk of relapse) due to high conformity. While available data so far does not show any clinical implications of these potential concerns, we should be vigilant about the same.

## Improvements in Verification

The uncertainties during setup of a patient and positional changes of the target make delivery of IMRT very challenging and warrant special considerations to minimize the same.<sup>28</sup> Keeping in mind this purpose, the recent era has seen advent and use of robust verification methods during delivery of IMRT. Modern RT machines that have integrated imaging technology for image-guided radiation therapy (IGRT) have come a long way to increase the precision of IMRT delivery.<sup>29</sup> With use of IGRT, radiation oncologists have become more comfortable and confident in using narrower setup margins, which allow reduction in the volume of adjacent normal structure that would have been otherwise exposed to the prescribed radiation dose with conventional wide margins. Clinically, this is translated to improved outcomes across many sites, recently shown in sarcomas (Radiation Therapy Oncology Group [RTOG] 0630).<sup>30</sup>

Various methods for target verification recently in use include electronic portal imaging device (EPID), kilo-voltage cone beam CT (CBCT), mega-voltage CBCT, CT on rails, each of them with its own set of advantages and disadvantages. EPID utilizes verification using bony landmarks or implanted radio-opaque markers in or adjacent to the tumors. For cross-sectional verification of target, where EPID is found to be inadequate, CBCTs are highly useful, with minimal and acceptable additional exposure of ionizing radiation. The use of higher energy CT (CT on rails) allows higher quality images with feasibility of adaptive planning on that set of CBCT images itself, although at a cost of higher exposure.

## Role of Adaptive RT

Use of CBCTs has shown that there are dynamic volumetric changes in tumor with RT in certain sites (having predominantly radiosensitive proliferative tumor cell population).<sup>31</sup> Use of conformal RT mandates we take care of such dynamic volumetric changes, so that there is no unwanted change in dosimetry. Dosimetric and nonrandomized studies have shown that replanning after significant regression of tumor is beneficial in certain tumor sites.<sup>32</sup> Integration of artificial intelligence in adaptive planning is an area of further exploration.

Although CBCTs are highly useful for most of the tumors, it is suboptimal in determination of soft tissue contrast. Integrated MR-LINAC, which has the facility for MR imaging in real time, for verification of soft tissue targets is a promising addition in the tools for image guidance in RT. Using specific sequences of MR for potential tracking of hypoxic areas of the tumor is also feasible, for localized dose escalation. Stereo-

tactic MR-guided adaptive RT has shown encouraging local control with favorable toxicity profile in high-risk lung tumors.<sup>33</sup>

In addition to the *interfraction* positional shift of target, *intrafraction* movement of the target, with a possibility of geometrical miss, is a notable concern while using conformal modern RT techniques. Various methods to counteract the same have been also developed and are being implemented.<sup>34</sup> These include breath hold techniques, active breathing coordinator, respiratory gating, and tumor tracking. Advent of four-dimensional CT scanners has helped to acquire high-quality planning CT images taking tumor/organ motion into account, enabling accurate estimation of tumor movement range.

## Emergence of Particle Therapy

The characteristic Bragg peak of particle beams, that allows highly precise dose distribution, makes it a very attractive RT modality. This has been exploited in a variety of tumors to enable dose escalation and/or to reduce late toxicities.

Starting its first clinical use in the Massachusetts General Hospital in the 2006, at present 99 centers across the world use proton therapy to treat cancers. There has been surge in the evidence for use of the same in various sites. Similar to what was seen in the transition from 3D-CRT to IMRT, use of proton therapy is encouraged by improvement in local control by feasibility of dose escalation and reduction of normal tissue effects (without any increase in low dose area unlike in IMRT).

Multiple dosimetric and phase II studies have shown improved disease control with proton therapy in sinonasal cancers, nonsquamous head and neck tumors like melanoma or adenoid cystic carcinomas, hepatobiliary malignancies, and low-grade gliomas. Owing to its favorable dose distribution profile and resultant excellent conformity, proton therapy has shown reduced treatment-induced toxicities in a wide range of cancers, including HNSCC,<sup>35</sup> mediastinal tumors,<sup>36,37</sup> pediatric medulloblastoma patients undergoing craniospinal irradiation,<sup>38</sup> low-grade or benign intracranial tumors,<sup>39</sup> and esophageal cancers.<sup>40</sup> A recent comparative study showed significantly improved toxicity profile with excellent oncologic outcomes with intensity-modulated proton therapy compared to that with IMRT in patients with nonmetastatic nasopharyngeal carcinoma.<sup>35</sup> Use of proton therapy is specially encouraged in pediatric patients, for possible reduction in second malignant neoplasms, attributable to the lower integral dose when actively scanned proton beams are used.<sup>41</sup> In certain sites (namely breast cancers, retroperitoneal sarcomas, gliomas, mediastinal tumors), comparative planning of photons with protons (including Normal Tissue Complication Probability [NTCP] modeling) is encouraged to determine probable benefit with protons.

Pioneered by National Institute of Radiological Sciences Japan since 1990s, heavy ion radiation combines the physical advantage of Bragg peak and a stronger relative biological effectiveness (RBE). The increased RBE is due to stronger cell kill via complex DNA damage, activated antitumor immune-

mediated cell deaths, and a few yet unelucidated biological mechanisms. This is clinically translated to excellent local control rates in the tumors deemed to be radioresistant<sup>42</sup> with acceptable treatment related toxicities. Intensity-modulated particle composite therapy using multi-ions is a very promising treatment modality currently under exploration.

Particle therapy necessitates a huge infrastructure cost. However, with the development of newer generation compact accelerators, more and more centers across the globe will be able to install particle therapy facilities. In the near future, we may expect triage of patients to receive photon, proton or heavy ion therapy based on the clinicobiologic features of tumor in each patient.

Potential limitations of particle beams include range uncertainties and sparse literature about organ tolerances (specially so with heavy ions). Range of uncertainties due to the traversing medium can be minimized to some extent by use of dual-energy CT simulator, as the attenuation information for the media is known better using two energies. Ongoing translational research aims to address such issues and help proper triaging of patients.

## Future Directions

With such tremendous technological developments, although outcomes with modern RT have improved significantly, local failures still remain a challenge to us. Biological aggressiveness of certain tumors that results in radioresistance is often the factor attributed to such failures. On the other hand, effective local control but increased rates of distant metastasis, possibly mediated by effects of radiation on immune system and/or on cell migration, is another hurdle toward receiving cures in cancer.<sup>43</sup> Efforts are underway to elucidate the detailed mechanism behind such failures and possible methods to prevent the same.

Similar to that with systemic anticancer therapy, there is a trend toward precision RT. This may include integrating genomic and molecular information to decide dose-fractionation, personalized OAR dose threshold derived using NTCP models, and use of personalized radiation sensitizers based on the tumor mutation profile, etc. Use of SBRT with targeted therapy and/or immunotherapy in neoadjuvant or adjuvant setting is a promising strategy aiming synergism between both the modalities, with potentially excellent local as well as systemic control.<sup>44</sup> RBE-based planning for particle therapy is another aspect in development. Similarly, FLASH therapy is a revisited RT option, with yet unelucidated molecular mechanism but promising outcomes.

## Conclusion: Optimal and Customized Usage Is the Key

We have come a long way in terms of technological achievements in the field of RT. This, as briefed above, has improved therapeutic ratio and has resulted in exciting clinical outcomes in various tumor sites. Appropriate use of the improved technology, combined with understanding and manipulation of the tumor biology, is likely to further improve the outcomes.

While being excited about the same, we should not forget about the gross disparity in the distribution of RT facilities in resource constraint areas. For the cancers widely prevalent in our country, timely access to even a simple telecobalt and a brachytherapy machine can reduce the mortality rates to a great extent, whereas for challenging cases, treatment using advanced technologies (that comes with an added infrastructural cost and skilled manpower requirement) may be worth, considering the relative benefit gained compared to conventional techniques. Hence, it is important to assess the cost-effectiveness and ensure appropriate triaging of patients for different RT techniques. Looking forward, we hope to ensure optimal access to basic RT facilities for all, and continued endeavors toward further improvement in outcomes using personalized RT.

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### Authors' Contributions

Both authors contributed equally to the work.

### Conflicts of Interest

None declared.

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