4 lines to 4 dimensions: The challenges ahead

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Radiation therapy in the modern era, has come a long way in the last 100 years, since its efficacy was shown to treat malignant lesions in the Radium and Roentgen era. The perception of the clinicians to be able to volumetrically encompass the tumour within the limits of 4 lines, circumscribing a square or a rectangular surface field, has also undergone a sea change with the understanding of the patterns of tumour spread, better diagnostic tools and radiobiological implications of the parameters, that have a bearing not only on the tumour control, but also on the morbidity of the adjacent normal structures. Coupled with these, is the gradual recognition of the need of organ preservation, both in terms of its anatomy and function, thereby ensuing an event free long term survival, along with a better quality of life. Thus, from radical surgical procedures involving en bloc resections of tumour and the adjoining normal structures, there has been a gradual shift towards less radical surgical procedures, supported by curative radiotherapy, producing similar outcomes.

Radiation therapy is thus steadily assuming the fulcrum of multimodality approach, in the management of most cancer patients. Accordingly, it becomes imperative for the present and the future radiation oncologists to brace themselves with the challenges, that the present state-of-art technology in radiation therapy promises to unravel. Truly, a transition from 4 line radiation therapy is in the offing and challenges anticipated, need active attention and consideration.

Radiotherapy is a physical modality that has been used to treat an aberrant biological process. Trying to achieve this objective, would be caught up with a multitude of problems. Nevertheless, the advancements made in the field of radiation therapy needs a closer perusal, so as to explore the best possible ways to effectively use the technical advancements made in the dose delivery, computation, display and synchronous adaptability of radiation treatment.

Developments in radiotherapy in the present era could be broadly grouped as, (a) innovations in diagnosis with treatment delivery technology and (b) biological and conceptual basis of radiation oncology. While the former has enabled clinicians to define the target in all its dimensions and the physicist to compute doses and monitor radiation delivery with precision, the latter has enabled one to understand the radiobiological principles that could be applied to design a prescription, using the three important variables of time, dose and fractionation, both for tumour and adjoining normal structures, to achieve an optimal therapeutic ratio. Thus, improvements in outcome for patients treated with radiotherapy could be achievable, once a symbiotic amalgamation of these two could be realized.

Innovations in diagnosis and treatment delivery technology – the challenge of target uncertainty

The transition from standard biaxial collimator systems to the various variants of multi-leaf collimators, has enabled one to shape the radiation portals beyond the traditional confines of merely defining beams, in terms of simple length and width, to encompass the target with three-dimensional conformality. Along with it, the capability of modulating the beam intensity through intensity modulated radiation therapy (IMRT), has been a step ahead, to further refine the dose intensity within the irradiated volumes, to maximize dose to tumour and spare the normal structures. Theoretically, it raises the possibility of dose escalation in tumours, which could be expected to improve tumour control.

However, as a prelude to undertake such conformation and IMRT, it becomes prudent for the clinicians to be certain of the geometric limits of the target. Even though dosimetrically, one can ensure coverage of the intended dose in the target within pixel accuracy, the same may not be applicable for target delineation. Although a host of diagnostic tools are available for target outlining, with options of multi-modalitly imaging using computed tomography (CT) or magnetic resonance imaging (MRI) and co-registration algorithms incorporated as a part of the present day radiation treatment planning software, the uncertainty in target delineation, especially for the gross target volume (GTV) and clinical target volumes (CTV), as defined by ICRU 50, could continue to pose a formidable challenge.
Neoplastic transformation and its progression in tissues is a complex biological event and results in both metabolic or functional and anatomical alterations in the tissues. The metabolic changes usually precede the anatomical distortions and when using CT or MRI or both, the tumour outline is based on these anatomical changes. The availability of functional imaging using positron emission tomography (PET) and its co-registration to produce hybrid anato-metabolic images, could therefore be a valuable means to draw the boundary limits on the gross and the clinical target volumes, to some degree of certainty. These are already being taken up for designing radiation doses and IMRT treatment plans.\(^[3]\) Hypoxic areas within the tumour, an important limiting factor in tumour control, could be selectively subjected to higher doses. Use of hypoxic fraction imaging with \(^{60}\)Copper labeled methylthiosemicarbazone (\(^{60}\)Cu-ATSM), with PET and intensifying doses at these hypoxic regions, have been explored recently in head and neck tumours.\(^[2]\) However, one would still be uncertain, since the anato-metabolic images would be a consequence of molecular alterations in the neoplastic cell milieu, which adds to the complexity of a true image of the real target. With the development of molecular biology diagnostic techniques and the introduction of DNA microarrays, one can hopefully look towards incorporation of molecular images, co-registered to the anato-metabolic images in the near future.\(^[3]\)

Till such time that molecular imaging becomes as an essential component in radiation therapy planning, one can adapt radiation therapy treatments, using the more readily available multivoxel magnetic resonance spectroscopy mapping of the tumour, or diffusion and perfusion images. Even within the GTV of the tumour itself, use of Blood Oxygen Level Dependent (BOLD) image, could demonstrate a gradient between the hypoxic and the oxic regions.\(^[4]\) These could be adapted in radiation therapy planning and IMRT effectively, to deliver a matching dose gradient to these regions of radiobiological significance.

Thus, conventional radiodiagnostic images could pave way for theragnostic images, which could form the basis of future radiation therapy planning. These theragnostic images not only could image the anatomical alterations, but also incorporate—metabolic images of important metabolites, geographically display hypoxic volumes within the target, tumour proliferation with nucleosides, or amino acids with PET, image clonogenic population using \(^{18}\)F FDG PET as a surrogate marker, permit molecular finger printing of known prognostic receptors e.g. EGFR and also image the functional critical normal structures.\(^[4,5]\) All these could provide valuable information for a true target delineation and permit a paradigm shift from the classical standard dose prescription based on anatomical target, to an individualized dose painting, tailor-made for each patient, a concept which has been shown to be technically feasible in clinical situations.\(^[2]\)

Perhaps, to be able to optimally translate the technological advancements in hardware, software and treatment delivery, the theragnostically demonstrated target volume has to be gradually adapted to modulate the treatment intensity through IMRT and lately to even guide and monitor radiation therapy delivery through image guided radiotherapy (IGRT). The challenge has now to be shifted in this direction.

Biologically optimized radiation therapy: Should it replace physically optimized radiation therapy?

The change from a physically homogenous dose distribution within the target volume, to deliberate incorporation of an inhomogenous dose profile within the target through IMRT; needs to be looked from its radiobiological implications. Evaluation through the physical dose volume histograms (DVH) may not always reveal the differences in the biological effective doses and the resultant effect on the normal tissue complication probability (NTCP), tumour control probability (TCP) and the uncomplicated tumour control probability (UTCP). This results from a differential dose per fraction and total dose, delivered to the various regions of the GTV, CTV and the organs at risk (OAR), within the same overall treatment time. Brahme,\(^[6]\) has very elegantly demonstrated the shift in the TCP and NTCP sigmoid response curves, with changes in the tumour stage with radiation. IMRT has been an effective tool to enable an increase of the therapeutic window, not through shifting the TCP curve of a conventional treatment to the left, but by pushing the NTCP curves further towards the right. Thus, even though the tumouricidal doses to control the tumour would remain the same, it is the reduction in dose to a significant volume of the normal tissue, that would be expected to improve the therapeutic ratio.

Use of multiple fields and inverse planning system for IMRT, has enabled a near optimum dose conformity within the GTV and a gradient of decreasing doses to the surrounding normal structures. A lower dose to the adjacent structures would indeed be expected, to reduce normal tissue complications. This is due to the well accepted fact, that the cell kill follows a linear-quadratic relation with increasing doses, which works well at standard clinical dose per fraction of 2 Gy. However, the demonstration of the phenomena, that at low doses (dose around 0.3 Gy per fraction), the resultant cell kill could be much steeper than previously realized, could complicate the issue. This low dose hypersensitivity has been demonstrated to be more pronounced for tissues with a large shoulder of the cell survival curve, as would be apparent for late responding tissues having a low \(\alpha/\beta\) value.\(^[6,7]\) Thus, even if the physical doses may be different, the ultimate biological effect as a consequence of the low dose hypersensitivity, could in effect be similar in regions of high dose irradiated, with a higher dose per fraction (as in tumour) and at regions of low doses exposed to a low dose fraction (as in regions of OAR). A gain in the TCP could be
at a risk of getting neutralized by a paradoxical increase in NTCP, even with lower physical doses.

Niemierko\textsuperscript{[8-11]} had tried to address the problems of the biological effect of inhomogenous physical dose distributions within the target, by introducing the concept of Equivalent uniform dose (EUD). This has been defined as the dose, which when distributed uniformly across the target volume, causes survival of same number of clonogens, as the delivered inhomogeneous dose. Modifications to the EUD has been proposed as “generalized EUD,” “modified EUD” and organ equivalent dose (OED).\textsuperscript{[8-11]} Thus, an effort is gradually being made, to formulate treatment plans not only on the basis of the physical dose profiles, but also on the biologically optimized treatment plans, taking into consideration, the resultant radiobiological implications of the heterogeneous dose distributions, deliberately sculpted through IMRT. The possible implications of these could be to design treatment prescriptions with a higher tumour dose and dose per fraction, but keeping the dose per fraction marginally lower for the normal tissues and avoiding an undue prolongation of overall treatment time. If desired, an associated tumour boost could be administered.

Biologically optimized radiation therapy (BORT) could thus become a formidable tool, which would indeed be the true amalgamation of the physical advantages of the dose delivery methodology, currently available for state-of-art radiation therapy and also the application of the knowledge of radiobiology gathered through not only \textit{in vitro} and \textit{in vivo} experimental data, but a wealth of clinical experience. BORT could also be an effective tool for undertaking a comparison of the alternate plans. Initial studies of computing the TCP, NTCP and UTCP, for various therapeutic plans, using 3D conformal and IMRT, reveal that BORT doses could be an effective tool to demonstrate the true therapeutic ratio through UTCP computations than conventional methods, with 3D conformal and IMRT physical doses.\textsuperscript{[12]}

Radiation therapy has thus moved a long way in the past century and improvements have been obtained through a conglomeration of the technological developments in equipment, computation, diagnosis and understanding the radiobiological implications. The journey which started with an empirical dose delivery, has progressed with the incorporation of conventional radiation therapy, demarcated by 4 lines (4 L) to 3D CRT, IMRT and even taking into consideration, the 4\textsuperscript{th} dimension (4D) of organ motion. A further refinement is expected to usher in an era of progressive treatment optimization – from physical to biological to molecular and predictive assay based radiation therapy. Till such time that these are put in clinical practice, one could take up the challenge to address the crucial 4D’s of radiation therapy. These include - Delineation of the target and organs at risks with certainty, with available theragnostic modalities, Determination of the optimum radiation dose – both physically and biologically, Determination of the optimum dose/fractionation, with emphasis on BORT for arriving at the best TCP, least NTCP and best UTCP and finally Dose delivery, that would demand constant precision from simulation to treatment completion.

The journey from 4L to 4D appears to have just begun and challenges ahead need to be met, to be able to exploit the benefits of the full range of therapeutic armamentarium, which is now at the disposal of the radiotherapy community.

REFERENCES


