

Is intensity-modulated radiotherapy for prostate cancer ready for prime-time?

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The integration of technology in medicine continues to transform patient care in terms of various important endpoints including treatment efficacy, efficiency, economics, and toxicity. The practice of radiation oncology has undergone substantial transformational change over the past two decades with the advent of several interlinked technologies. Classical radiation oncology treatment techniques were generally planned using two-dimensional (2-D) techniques. The use of these 2-D techniques significantly limited the maximum dose to the cancer target(s) due to the addition of large safety margins for target/delivery uncertainty as well as the lack of conformal avoidance of normal tissue dose to radiosensitive structures.

Newer technologies have improved the targeting of cancer (e.g. CT, MRI), the conformality of radiotherapy (three-dimensional conformal radiotherapy – 3-DCRT, intensity modulated radiotherapy - PBRT, low-dose rate and high-dose rate brachytherapy, and proton-beam radiotherapy - PBRT) and the accuracy/precision of treatment delivery (patient immobilization, fiducial markers, and image-guided radiotherapy - IGRT). All of these technologies work to optimize

the therapeutic ratio between the positive anticancer effect of radiotherapy on macroscopic and microscopic disease and the negative normal tissue effects leading to both acute and late radiotherapy toxicities. In the context of prostate cancer radiotherapy, these technologies attempt to improve cancer endpoints such as biochemical control and overall survival by escalating dose to the prostate and minimizing dose to adjacent radiosensitive structures such as the rectum, bladder, and penile bulb.

In this issue of *The Canadian Journal of Urology*, Ohri et al report on a systematic review and meta-analysis of late toxicity effects as measured with a standardized late radiotherapy toxicity scale.¹ They report that IMRT and PBRT external-beam radiotherapy was associated with significant declines in reported severe GI toxicity when compared to 3-DCRT. Also, they confirmed that prostate dose-escalation can be related with additional moderate and severe late toxicity. Both these findings confirm the importance of therapeutic ratio optimization in order to attempt to deliver maximum dose to the prostate target while using advanced radiotherapy delivery technologies to reduce normal tissue dose.

Recently, Cancer Care Ontario commissioned a series of systematic reviews to assess the indications and evidence related to the implementation of IMRT in a series of tumor sites including prostate cancer (www.cancercare.on.ca). Bauman et al found that a review of the available evidence demonstrated equivalence or superiority of IMRT over 3-DCRT dose-escalated (> 70 Gy in 2 Gy daily fractions) external-beam radiotherapy

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techniques in terms of acute and late genitourinary (GU) and gastrointestinal (GI) side effects for the treatment of primary non-operative disease.² Given the published evidence supporting the use of dose-escalated radiotherapy for improved disease control, this practice guideline recommended the routine use of IMRT over 3-DCRT for the radical dose-escalated treatment of localized prostate cancer.

Further supporting these findings is the recent presentation of preliminary results from the Radiation Therapy Oncology Group 0126 prostate dose-escalation trial at the plenary session of the 2011 American Society of Radiation Oncology annual meeting. A toxicity analysis comparing patients treated with IMRT versus 3-DCRT on the dose-escalation arm of the trial (79.2 Gy in 1.8 Gy daily fractions) was performed prior to final reporting of the primary endpoint of overall survival.³ Michalski et al found that IMRT dose-escalated radiotherapy was associated with statistically significant reductions of acute grade two or greater GI and GU toxicity as well as a 26% reduction of grade two or greater GI toxicity. Excessive dose to the rectum which was found to be inter-related with 3-DCRT/IMRT technique was found to predict for late GI toxicities.

Moving forward, other questions still remain unanswered in prostate radiotherapy which will require the completion and reporting of randomized clinical trials. Such questions including the role of hypofractionated radiotherapy and stereotactic ablative radiotherapy (SABR) in delivering relatively few (5-20) high-dose fractions to the prostate, the role of pelvic radiotherapy in intermediate- and high-risk disease, as well as the optimal indications of prostate brachytherapy (with or without external-beam radiotherapy) versus external-beam radiotherapy alone for patients selecting non-operative management of their prostate cancer. New innovations in radiotherapy technique need to be assessed for both treatment efficacy and for normal tissue toxicity to demonstrate improvements in the therapeutic ratio prior to widespread adoption. □

References

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