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EDITORIAL

Improved Long-Term Outcomes With IMRT: Is It Better Technology or Better Physics?

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Intensity modulated radiation therapy (IMRT) for the treatment of localized prostate cancer has now been in use for almost 15 years. There has been evidence during this time that this form of treatment delivery is more accurate and is associated with fewer side effects compared with previous forms of radiation therapy applications. Zelefsky et al (1) reported their observations over a decade ago that acute and late rectal side effects were significantly reduced after high-dose IMRT compared with historical controls treated with 3-dimensional conformal techniques (3D-CRT) to similar dose levels. More recently, they have noted that these differences in toxicity outcomes persisted with follow-up beyond 10 years (2).

In this issue, Michalski et al (3) report on the toxicity outcomes of Radiation Therapy Oncology Group (RTOG) 0126 and provide for the first time evidence that IMRT-treated patients experience less toxicity after therapy than do a concurrently treated cohort of patients treated with similar doses with the use of 3D-CRT. It is important to note that although RTOG 0126 never intended to compare IMRT with 3D-CRT, thanks to a later amendment in the protocol that allowed practitioners to use IMRT for accrued patients, an opportunity eventually existed to compare these 2 cohorts of patients retrospectively. Notwithstanding significant differences in the treatment volumes between the IMRT and 3D-CRT cohorts and in the margins used to create planning target volumes, these investigators still noted that the combined gastrointestinal and genitourinary toxicities were lower among the IMRT-treated patients.

Yet, what is most revealing about this study is that when the authors performed a multivariable analysis for predictors of toxicity and added dosimetric-based variables to the regression model, the treatment technique was no longer a significant factor. The authors found instead that dosimetric parameters were the most important predictors of late toxicity—namely, that a dose of >70 Gy to more than 15% of the rectal volume was an independent predictor for late grade 2 rectal toxicity ($P = .034$). These findings suggest, as we expected, that a critical predictor of late toxicity after radiation therapy was the volume of normal tissue exposed to the high doses of radiation therapy. Conformal delivery systems such as IMRT may simply represent a means to achieve that aim—a meaningful reduction of the volume of rectum exposed to the high doses of irradiation.

We believe there is an important message here. There is nothing magical about 3D-CRT, IMRT, image guided radiation therapy, or novel radiation therapy delivery systems and no guarantee that these approaches spare the patient from toxicity. Yet, these delivery systems are all important means to achieve the end result of applying a high dose of irradiation with concomitant reduction of exposure to normal tissue. Recently it has been reported that enhanced accuracy using daily image guidance with the placement of fiducial markers resulted in *less* urinary toxicity during the application of ultra-high-dose radiation therapy (4). This observed reduction in toxicity was achieved without a tightening of the margins used around the clinical target volume. Conformality enhancements in the delivery of radiation therapy have facilitated improved dose distributions and greater accuracy of treatment. Accordingly, this allows the radiation oncologist to safely deliver the required high radiation doses into the tumor.

In the study by Michalski et al (3), the IMRT cohort in general was actually treated with a larger high-dose target volume according to protocol stipulations; yet, despite that requirement, treatment was associated with a 27% *reduction* in late gastrointestinal toxicities. It appears that the reason for this may be related to IMRT more effectively and more frequently being able to reduce the V70 exposed to 15% or more of the rectum. This is

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consistent with the QUANTEC recommendations that the volume of rectal high dose overlap in the treatment plan be constrained to V70 <20% and V75 <15% (5). Furthermore, studies that attempt to reduce the risk of treatment-related rectal toxicities after radiation therapy should consider the incorporation of dose−volume endpoints such as the V70 >15% of the rectal volume for identifying patients in whom rectal toxicity may more likely develop after conventionally fractionated IMRT.

Although these findings underscore the benefit of using IMRT to achieve greater conformality to obtain the desired dosimetric outcome, they also suggest that some patients with "geometrically favorable target volumes" that do not significantly overlap with the rectum may safely receive high-dose radiation therapy without the need for IMRT. On the other hand, patients who are identified as being at high risk for rectal toxicity (by virtue of the fact that despite careful planning they still receive V70 Gy >15% of the rectal volume) may benefit from interventions and new technologies currently being tested to improve the geometry of the rectum and its juxtaposition with the target volume. For instance, physical manipulation methods have also been suggested that could potentially reduce rectal toxicity. Prada et al (6) have reported reduced rectal toxicity based on endoscopic posttreatment evaluations with the transperineal injection of hyaluronic acid in the space between the anterior rectal wall and the posterior aspect of the prostate to create a greater separation between these 2 organs. More recently, several investigators have shown marked reduction in rectal wall doses with the transperineal insertion of a biodegradable balloon that could provide a separation of as much as 1 cm, effectively reducing rectal doses during radiation therapy (7, 8). Thus, the use of IMRT does not routinely prevent rectal toxicity; however, with a carefully designed treatment plan, effective image guidance, and potential "man-made" improvements in the geometry of the target and organs at risk, it is an effective tool for producing a superior dosimetric outcome.

Although Michalski et al (3) have shown reductions in rectal toxicities, it seems that IMRT has not yet effectively reduced bladder-related toxicity after high-dose radiation therapy. In the Memorial Sloan-Kettering Cancer Center experience, reduced urinary toxicities after radiation therapy to the prostate have also not been observed with the use of IMRT (1, 2). These findings may be related to our ignorance of the critical anatomic component or subunit responsible for post-radiation therapy bladder-related toxicity. The recent observation of reduced urinary toxicity with image guided radiation therapy could possibly be related to less dose delivered to the bladder trigone rather than any relationship to whole bladder or urethra doses (4). Acute symptoms could possibly be related to swelling and inflammation to the prostatic urethra, but late toxicity may more likely be related to bladder neck and dose to the trigone region. In a recent analysis we observed that dose to the trigone was in fact an independent predictor for late grade 2 urinary toxicity after high-dose IMRT (unpublished data). Clearly, this endpoint requires further study.

The resurgence of interest in proton therapy for prostate cancer has also raised interesting questions about the potential for this technology to reduce the risk of late toxicity after treatment. The Bragg peak effect of protons poses a unique biologic advantage for reducing the integral dose and exposure to normal tissues. Yet, to date there is no convincing evidence that this inherent advantage of the proton beam has translated into reduced late complications or secondary malignancies for prostate cancer patients. Techniques for improving conformality of the proton beam with intensity modulation in proton therapy and with adaptive image guidance remain in their infancy and will certainly require more research and clinical experience. In the meantime, the results of ongoing prospective studies comparing outcomes between IMRT and proton therapy for patients with prostate cancer will help sort these issues out.

It is likely that new developments in treatment planning and delivery systems have reached a plateau, and it is unclear whether any new radiation therapy intervention or technique will produce further dramatic reductions in side effect profiles of treated patients. Radiation therapy may only produce further reductions in side effects with the recognition or identification of the critical elements of the normal tissue structure or dose patterns most closely associated with treatment-related dysfunction. This information would then need to be used to drive accurate image guided interventions. In the future, with the help of functional imaging and biologically based outcome-driven treatment planning, we may need to explore image guided *dose de-escalation* in the critical locations to have a more meaningful impact on reducing toxicity after radiation therapy for prostate cancer while making a real difference in quality of life for our treated patients.

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