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EDITORIAL

Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Less Cost at the Expense of More Genitourinary Toxicity Is a Concerning But Testable Hypothesis

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See accompanying article on page 1195

While randomized controlled trials (RCTs)[1-2] show that prostate-specific antigen (PSA) –based screening reduces death from prostate cancer (PC) and this effect appears to be more pronounced in younger and presumably healthier men[3] (number needed to treat of 12 at a median follow-up of 14 years[2]), the US Preventative Task Force has concluded that screening for PC with PSA does more harm than good.[4] Why? While it has been suggested in one RCT (Prostate Cancer Intervention Versus Observation Trial [PIVOT])[5] after a median follow-up of 10 years that treatment of low-risk PC,[6] which is detected more often with PSA screening,[1,2,7] does not lead to a reduction in death from PC, the treatment effect for all men in the study approached significance ($P = .09$) in reducing death from PC. This was observed despite being underpowered (designed to accrue 2,000 but accrued only 731)[5] and enrolling men of less than average health based on a comparative SEER program study.[8] Therefore, should these results at a 10-year median follow-up be used to decide on treatment for healthy men whose remaining life expectancy is greater than 10 years?[9] Probably not, yet this data has been used to deter PSA screening and has prompted active surveillance in men diagnosed with low-risk PC[6] who are healthier than men in PIVOT.[5]

While screening for and subsequent treatment of PC in men with limited life expectancy due to comorbidity has led some men to experience treatment-related toxicity without expectation of avoiding metastasis and death from PC termed "over diagnosis and over-treatment"[10] respectively; is this a reason to abandon PSA screening altogether? The concern is that not screening high-risk patients, such as healthy African American men who are at higher risk of harboring and dying from aggressive PC[11] compared with other races and ethnicities, might lead to more advanced disease that is less amenable to cure. We know that these advanced cancers are less likely to be cured despite multimodality therapies which are more toxic then unimodality therapy, which is often curative when the disease is PSA detected. Moreover, is this a reason to tell an otherwise healthy man who has been diagnosed with "low risk PC"[6] that he does not need treatment when, due to prostate needle biopsy sampling error, 25% of men with biopsy proven "low-risk PC[6]" are found to have at least intermediate risk PC[6] after undergoing radical prostatectomy (RP)[12] and when for such men PIVOT[5] suggested a reduction in death from PC when RP was offered?

The unfortunate result of these claims regarding screening for and treatment of PC is that some men facing a diagnosis of PC are requesting de-escalation of, or no immediate treatment for, their PC in an effort to avoid the possibility of experiencing toxicity without clinical benefit or overtreatment. To that end, treatments such as focal ablation[13] and shortened (or accelerated) courses of radiation therapy using cyberknife or stereotactic body radiation therapy (SBRT)[14] are being studied, however randomized evidence of comparable toxicity and efficacy compared with accepted standard of practice are currently unavailable. Of concern, while only a theoretical basis for improved local control with accelerated radiation treatment exists,[15] this approach is being used to treat men with PC off study. It is possible this treatment could be less efficacious and more toxic then current standards of care.

Fortunately, data are currently pending from an ongoing Swedish RCT (International Standard Randomized Controlled Trial Number Register 45905321)[16] evaluating the relative efficacy and toxicity of an accelerated RT regiment with high-dose intensity-modulated radiation therapy (IMRT) which is a standard of care as endorsed by the 2013 National Cancer Center Network guidelines.[6] Specifically the two randomized treatment arms are 78 Gy in 39 conventional 2 Gy IMRT treatments over 8 weeks versus 42.7 Gy in seven hypofractionated or accelerated 6.1 Gy SBRT treatments over 2.5 weeks for primarily intermediate-risk PC.[6] Importantly, toxicity reporting from this RCT is expected by 2015.

While awaiting the results of this RCT,[16] the study by Yu et al[17] that accompanies this editorial evaluates the relative toxicity of these two approaches. They used the Chronic Condition Warehouse database, which is a comprehensive database of 100% of Medicare fee-for-service claims for patients with specific conditions such as PC. They then performed a 2:1 match (IMRT to SBRT) within each follow-up

interval of 6, 12 or 24 months using the Mahalanobis matching technique[18] by age, race, residence in a metropolitan county, comorbidity, receipt of androgen deprivation therapy (ADT), income and prior influenza vaccination as well prior visit to a primary care provider to create the data set for analysis. They used a random effects logit model[19] adjusting for age, comorbidity and ADT use to estimate the adjusted odds of toxicity at 6, 12 and 24 months for men treated with SBRT as compared with IMRT.

They generated the concerning but testable hypothesis that SBRT has more genitourinary (GU) toxicity but is less expensive than IMRT, after accounting for the cost of the increased GU toxicity observed with its use.[17] Specifically, they show in their Table 2 that GU complications were significantly increased for men treated with SBRT versus IMRT with adjusted odds ratio (AOR): 1.29 (95% CI, 1.05 to 1.53); $P = .009$; AOR: 1.23 (95% CI, 1.03 to 1.43); $P = .01$; and AOR: 1.38 (95% CI: 1.12 to1.63); $P = .001$ at 6, 12, and 24 months respectively. Also, as shown in their Figure 1[17] the respective increase at 6, 12 and 24 months in the rates of GU toxicity for SBRT as compared with IMRT was 3% (15.6% *v* 12.6), 3.9% (27.1% *v* 23.2%) and 7.6% (43.9% *v* 36.3%).

It is important to recognize that Yu et al[17] generate a testable hypothesis and not proof of causation because these results are nonrandomized and there are several patient and treatment factors[20-22] that could have influenced the results. In this regard, the authors could not adjust for such factors because the information was not available; namely, baseline GU and GI function, dose fractionation schemes employed for IMRT and SBRT, dose volume constraints used and whether these were achieved or violated, expertise of the physics staff involved in quality assurance of treatment delivery, medication use such as anticoagulants, and prostate gland volume.

They also could not adjust for the use of pelvic RT which can contribute to higher GI toxicity.[23] However, they note that since more men undergoing IMRT as compared with SBRT received supplemental ADT that they were more likely to have high-risk PC.[6] As a result, some men during the study period may have been treated using both ADT and pelvic RT. Although the matching method[18] and multivariate model[19] that adjusted for ADT use should have adjusted for pelvic RT use if it was always used with ADT, it is possible that some men undergoing IMRT could have received pelvic RT without ADT, which would tend to increase the overall GI toxicity of IMRT compared with SBRT, creating concern for the observed increase in GI toxicity at 6 months in men treated with SBRT as compared with IMRT.

Finally, the absolute rates of GU toxicity for men treated with SBRT as compared with IMRT were high and do not reflect clinical experience to date for IMRT[24] or SBRT[13] use with regard to clinically significant GU toxicities such as urethral strictures, urinary incontinence, and obstruction. These numbers may be inflated because they were not able to measure the grade of toxicity. Therefore, if these percentages include mostly grade 1 toxicity the clinical significance of the results remain difficult to assess. They also included diagnostic procedures such as cystourethroscopy and complex uroflowmetry, which may have been performed for an issue that was not treatment related. Nevertheless, the same metrics were used to assess toxicity rates across the two modalities so the increasing difference in GU toxicity over time following SBRT versus IMRT may still have merit.

Therefore, when treating men with PC, is it acceptable to recommend a more convenient treatment that takes less time and is less expensive despite the possibility of increased toxicity and unknown comparative efficacy to current standards of practice? I do not think so.

In conclusion, despite the potential limitations of the study by Yu et al[17] including the lack of adjustment for important patient and treatment factors in the model and the inability to assess the grade of the GU complications, the results of the current study should raise our awareness that the potential for an increase in clinically significant GU toxicity with SBRT as compared with IMRT exists. As the authors allude to in their concluding remarks, I would also recommend that until the results of the Swedish RCT[16] are available to provide data about the relative efficacy and toxicity among men treated with IMRT versus accelerated RT, accelerated RT regiments utilizing cyberknife or SBRT for PC should only be performed in the setting of well-designed clinical trials.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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