Re: Proton vs Intensity-Modulated Radiotherapy for Prostate Cancer: Patterns of Care and Early Toxicity

Yu and colleagues used the Medicare billing database to compare intensity-modulated radiotherapy (IMRT) to proton beam radiotherapy (PRT) (1). Unfortunately, this comparison is difficult because of the nature of the groups compared, data within the database, retrospective study design, and various biases. Inherent to this analysis was the attempt to make valid conclusions about endpoints this database was not designed to measure. The most valid conclusion was that PRT was more expensive.

Regarding the statement, “Patients were assigned to the PRT group if there were any codes for PRT delivery,” the methodology of including PRT patients who had any PRT may have introduced bias. It is likely that some patients received PRT as a boost after photon radiotherapy (RT). These appear to have been included in the proton group. Patients treated in this manner generally received two-thirds of their radiation as photons. Their inclusion would bias the study, making interpretation incomprehensible. Assuming they were assigned to the PRT arm, they would likely have more toxicity because greater volumes of bladder and intestine would have been irradiated than with PRT alone. Because the majority of their dose was photons, the results would be more likely to reflect photon therapy.

Toxicities included that appear unrelated to radiotherapy include genitourinary infection, upper tract dysfunction, and systemic derangements. Including toxicity codes that are likely unrelated to radiotherapy serve to make the outcomes appear more similar than different. The most frequent radiotherapy toxicities are irritative bladder and rectal voiding side effects, which were not considered in this analysis. Also left out was bleeding that did not result in transfusion, which is a common toxicity. Leaving out the more common side effects/toxicities would also make the outcomes appear more similar than different.

The problem with the statement, “This study represents the most robust comparison of early toxicity for PRT vs IMRT for prostate cancer to date” is that this study is not robust. The authors did not include the majority of RT-related toxicity and included toxicity unrelated to RT. Then, they make the conclusion that this is robust, whereas the prospective clinical data suggest extremely low risk of PRT-related toxicity (2,3). The Medicare databases do not contain clinical materials necessary to measure these outcomes accurately. Thus, the conclusions are at best suspect. The potential harm of inaccurate conclusions is that prospective payers and patients may believe the authors’ conclusion regarding the relative toxicity of PRT compared with IMRT. The authors create controversy, which may result in fewer patients being treated with a potentially less toxic therapy because of inconclusive data based on data from billing databases rather than high-quality clinical documentation. We agree with the authors that more high-quality data are needed regarding PRT. Fortunately, excellent prospective data are available, and a randomized study comparing these modalities is open (2,3).

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References

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Response

We appreciate the comments of Schild et al. and the opportunity to respond. They raise three concerns: that patients who underwent proton radiotherapy (PRT) for prostate cancer also underwent photon radiotherapy and that the toxicity attributed to PRT may actually reflect photon therapy; that some recorded toxicities were unrelated to radiotherapy; and that the less severe and more common side effects of radiotherapy, such as irritative bladder symptoms and rectal voiding, were not included.

Regarding their first concern, only less than 3.2% of patients in the 12-month sample who underwent PRT received photon therapy. The lack of difference in complications between PRT and IMRT in our study is unlikely to be due to this small subset of patients.

Regarding their second concern, in order to measure the toxicity of treatment in the most comprehensive manner possible, we a priori included all Medicare claims indicative of complications potentially due to radiotherapy. Though Schild et al. question whether some of these complications are truly related to radiotherapy, this should not bias our results, as it is unlikely that there would be differential ascertainment of these outcomes between treatment groups.

Regarding their third concern, the toxicities measured from Medicare claims represent those that came to medical attention, likely representing a higher “grade” of toxicity than irritative symptoms and other toxicities not brought to medical attention. However, we applied the same approach to ascertaining toxicities for both treatment arms, matched patients on a range of clinical and demographic variables, and conditioned our analysis on the matching. For our results to be biased away from higher complications in the IMRT group and towards the null, any underreporting would have to be more common in the IMRT arm despite matching, which seems unlikely.

Consistent with our findings, no other comparative study to date has shown a durable benefit to PRT in comparison to IMRT. In one nonrandomized study of 93 patients who underwent PRT and 153 patients who underwent IMRT, there was only a transient difference in patient-reported quality