Reviewer's report

Title: Measurement of Skeletal Related Events in SEER-Medicare: A Comparison of Claims-Based Methods in Men with Metastatic Prostate Cancer

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Reviewer: Sandip M Prasad

Reviewer's report:

The authors provide a valuable review of methodology to measure skeletal-related events (SREs) using multiple different approaches in SEER-Medicare datasets. To measure SRE prevalence, two definitions for SREs were utilized: 'base case' 21-day windows (most commonly used in the literature and by the FDA) and 'alternative' in which different claims and time periods were used to identify each type of SRE, focusing on claims for spinal cord compression, pathologic fracture, surgery to bone, or radiation (suggestive of bone palliative radiation). Their findings demonstrate a small but real 8% difference between the two definitions, underscoring the importance of methodological approaches as SREs are a critical and measurable composite endpoint in many advanced prostate cancer studies.

This is an important and well-written manuscript. My reviewer comments are below:

Major Compulsory Revisions

1) None

Minor Essential Revisions

1) None

Discretionary Revisions

1) The authors excluded "other fractures" associated with falls or accidents on another level within 14 days of such documentation as they report that the fall was the causative agent rather than disease. While I think this is reasonable, in practice, the majority of patients with falls may not have this event actually coded accurately into the medical record; in addition, I would argue that a fall leading to a fracture in a patient with metastatic prostate cancer may in many instances be appropriately categorized as an SRE if additional clinical data were provided. I would be interested in the number of excluded "other fractures" and whether or not their inclusion would alter the findings.

2) Can the authors provide the ratio of claims data in SEER-Medicare during the study period for men with primary prostate cancer treatment with 2-dimensional and 3-dimensional radiation, intensity modulated radiation therapy, and stereotactic radiosurgery so that their claims about the relative use of each form
for prostate vs. bone therapy can be assessed? I would also be interested in the incidence of prostate radiation in RCTs in men with metastatic prostate cancer to establish a baseline of this activity as in my experience this is relatively uncommon.

3) The assessment of choosing a code definition to use for computing the SRE cumulative incidence is, in my opinion, the greatest departure between using claims data and trial data. As the authors note, in population-based analyses, these definitions reflect utilization and claims dates are associated with service rather than diagnosis. It is unclear in which direction this may bias the results (+ 7 days or - 7 days).

4) While a critical component of the measurement of SREs, the assessment of the use of radiation appears most methodologically unsound and variable. This, while a limitation, is actually an important finding of the study and should be presented as such.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests