Reviewer's report

Title: The use of early postoperative prostate-specific antigen to stratify risk in patients with positive surgical margins after radical prostatectomy

Version: 2
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Reviewer: Thomas J Sebo

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GENERAL COMMENTS:
This study assesses the role ultrasensitive serum PSA testing after radical prostatectomy (RP) has in patients with positive surgical margins (PSM). In a study of 116 consecutive patients (after eliminating 67 patients [37%]), the authors assessed ultrasensitive serum PSA testing at 14, 30, 60, 90, and 180 days to determine the predictive power of who would develop biochemical recurrence (BCR) defined as serum PSA ≥0.2 ng/ml by calculating areas under the ROC curves. Their conclusions were that only ultrasensitive serum PSA assessment at 30 days and beyond were capable of stratifying patients into the appropriate group of “treatment” versus “no treatment” by radiation after RP. The authors showed that their model decreased the risk of over-treating with adjuvant radiation in 53% of their patients. Conversely, of 28% of patients theoretically at risk for undertreatment (i.e., no adjuvant radiation), 86% of these patients would have been captured with their model at 90 days.

The authors are to be congratulated for a very nice, clean study. There are some specific comments I would like to see addressed, however, before considering publication. They are as follows –

SPECIFIC COMMENTS:
The following comments are major compulsory revisions – 2, 7, 8, 10, 12, 13, and 19

The remaining comments are minor, essential revisions. There are no discretionary revisions.

1) Line 69 – “specimens,” not “specimen”
2) MAJOR COMPULSORY REVISIONS: Lines 80 and 81 – the authors state that not all patients with PSM develop BCR; however, not all patients with BCR develop true cancer progression. Therefore, the authors’ stated desire to correctly identify those patients most likely to benefit from adjuvant management needs to take the next step of ferreting out those patients whose BCR leads to local/ systemic progression and cancer-specific death.
3) Line 97 – “remaining” and not “remained”
4) Line 110 – “Of these 183 patients, 63,” not “Out of them, 63”

5) Line 113 – “patients treated with neo-adjuvant hormonal and/ or radiation therapy,” rather than “patients with the evidence of hormonal therapy and/or radiotherapy”

6) Line 140 – “statistically significant,” not “statistical significant”

7) MAJOR COMPULSORY REVISIONS: Line 108 – the authors indicate that they derived their cohort from patients who pre-operatively contained clinically localized prostate cancer. Please expand on this – e.g., how many were T1c, T2a, T2b, and T2c? This could make a difference in terms of the surgical approach by the urologist – specifically, extrafascial, fascial, or intrafascial extirpation of the prostate gland; and this, in turn, can impact on whether the surgical margin will be positive, above and beyond its pathologic stage at surgery.

8) MAJOR COMPULSORY REVISIONS: Lines 142 – 143 – the authors indicate that follow ranged from 6 to 69 months with median follow-up of 31.4 months. That is 0.5 years to 5.75 years. While that is long enough for assessment of BCR, it is a bit short for more significant outcomes including systemic progression and death due to prostate cancer. Admittedly, the intent of the study was to assess the role of ultrasensitive PSA testing in the context of BCR and adjuvant radiation therapy. However, the missing piece of the study is whether the immediate addition of radiation makes a difference in final outcome.

9) Line 147 – “Except at day 14,” not “Except at the day 14”

10) MAJOR COMPULSORY REVISIONS: Lines 149 and Table 1 – in reference to Table 1, the table is clean and easy to read. However, I would like expansion of the term “Pathologic extracapsular extension.” Do the authors mean pT3a or pT3a and b?

11) Line 156 – “Apart from non-significant,” not “Apart of non-significant”

12) MAJOR COMPULSORY REVISIONS: Lines 173 – 178 – the authors make a few assumptions in this paragraph, which, in essence, is at the heart of their study: Namely, what difference does the application of radiation therapy play in ultimate outcome in these patients – or, at the very least, what did the addition of radiation do to the patients’ serum PSA values? Admittedly, the authors set up the argument well in their Introduction, but, in the final analysis, there is a little bit of circular arguing if the goal is to reduce the serum PSA level below 0.2 ng/ ml when we know upfront that the majority of these patients do not ultimately die from prostate cancer.

13) MAJOR COMPULSORY REVISIONS: The other point that is begged in this paragraph and, in essence, throughout the study is the nuances of a positive surgical margin (PSM). As the authors astutely suggest, it’s not just PSM, yes or no, it’s where the margin is positive, how many margins are positive, and what the extent of margin positivity is, as well as other details such as Gleason pattern of cancer at the margin, cautery effect, etc. These are factors which could also play a significant role in predicting who will progress to not only BCR but also
systemic progression and prostate cancer specific death.

14) Line 184 – “cancer in the last decade,” not “cancer in last decade”

15) Lines 185 – 186 – “Comparable results were found in the present study,” not “Compatible results were found in present study”

16) Line 202 – “Several explanations may explain,” rather than “Several explanations were suggested in order to explain”

17) Line 207 – “impression of a PSM,” rather than “impression of positive surgical margin”

18) Line 210 – “in the surgical bed who would be the best candidates for immediate adjuvant treatment” rather than “in surgical bed, those patients who would be the best candidates for immediate adjuvant treatment”

19) MAJOR COMPULSORY REVISIONS: Line 218 – while it is true that there is no general consensus on how to report PSM, this does not obviate the need to collect more detailed information so as to begin the process of building an argument for or against the role of said information in the reporting and subsequent management of a PSM. In other words, it strikes me as “logical” that a PSM that is focally involving a cauterized posterior inked margin is likely to be predicted by their model not progress and, as such, require radiation therapy. This, in turn, might eliminate the need for more testing with an ultrasensitive PSA marker. Ultimately, we have no way of testing this hypothesis based upon the authors’ study parameters.

20) Lines 220 – 221 – not sure I completely agree with this statement as some institutions can clear surgical margins via frozen section analysis and, as such, eliminate PSM from multivariable models in predicting who will develop BCR and death due to prostate cancer.

21) Line 234 – eliminate “already” before “…at day 14”

22) Lines 236 – 237 – please change to read “However, as time from surgery increased, the predictive power of ultrasensitive PSA measurements increased. For example, the calculated AUROC curves for day 30 and day 60 were 74% and 84%, respectively.”

23) Line 254 – change to read “1 of 16 patients

24) Line 258 – remove comma after argued

25) Conclusions – needs to be reworked something as follows: The present study provides insights into the role ultrasensitive serum PSA measurements plays in determining who will develop BCR and, as such, be candidates for early radiation and/ or hormonal therapy. The kinetics of post-RP serum PSA decline may allow better stratification of patients who would benefit from immediate radiation therapy.