Reviewer’s report

Title: Disease-specific outcomes of Radical prostatectomies in Northern Norway; a case for the strong impact of perineural infiltration and postoperative PSA-doubling time

Version: 2  Date: 7 December 2013

Reviewer: Andreas MAR Røder

Reviewer’s report:

First of all, I want to thank the authors for giving me the opportunity to review the interesting paper entitled: “Disease-specific outcomes of Radical prostatectomies in Northern Norway; a case for the strong impact of perineural infiltration and postoperative PSA-doubling time”.

They have done a tremendous effort by putting this together.

Major Compulsory Revisions

1. I think the paper is too “wordy”, sometimes even confusing. Especially the M&M and Results section should be more stringent. There is too much argumentation for the use of specific methods, e.g. PSAdt. For example, why mention that calculation of PSAdt may not be straight forward, when its not discussed in the Discussion?

2. The result section should be more prose style and not repetition of all the data in the tables.

3. Using a combination of local and distant failure as CF is somewhat intriguing. For the patient, there is a huge difference, because local failure is still curable, whereas distant failure is an potentially incurable disease an have serious implication for the patient with an immense probability of receiving endocrine therapy with a number of side-effects. How would the authors translate the event CF to their future patients based on this analysis? I think it’s difficult. Distant failure is the most clinically relevant endpoint. And this endpoint is susceptible to severe bias, especially surveillance bias and indication (for scans) bias. This, however, is to some extent mentioned by the authors.

4. Figure 2+3 is in my opinion flawed. PCa-specific survival should not be calculated from the date of BF to death but from the date of surgery. KM analysis is bases on right-censored time to event analysis and results in a probability of being without an event from time t(0) to t(x). By excluding patients without BF the analysis will overestimate the probability of an event.

The authors have to remember, that although some patients have not yet experience an event, they are still at risk of an event. Therefore, all patients should be included when analyzing the probability of being without an event (KM) or the hazard of an event (Cox).
5. Regarding Cox proportional hazard model
I hope the Cox model used do not use the same methods as the KM analysis, i.e.
only include patients with BF. In such case, it should be re-done.
PSA should be analyzed as a continuous variable on a logarithmic scale in order
not to violate the rule of normal distribution.
I think multivariate analysis on 15 events is not appropriate and should be
considered taken out.
6. Why not use Gleason >=8 as one variable?
7. I am skeptic about the PSAdt calculation. First of all, it is based on very few
measurements and therefore the risk of misclassifying patients with the “true”
PSAdt is eminent (there are a number of papers on this issue, the latest by
Thomsen FB, BJUI 2013). Next, the analysis is based on very few events and
therefore extreme 95%CIs is obtained. Also, why use backward selection? How
would the authors explain their results to their future patients – in layman’s
terms? Do you really think that PSAdt “outperforms Gleason score” or is it a
matter of statistical “problems”?
8. Line: “This is the first large Scandinavian multicenter study presenting the
impact of prognostic variable information regarding BF, CF and PCD in
Scandinavia in the PSA era”.
This statement is not correct. A number of Danish and Swedish studies have
been published.
Minor Essential Revisions
9. Line: “There has been an increasing use of radical prostatectomy (RP), but a
majority of patients diagnosed with PC will not have symptomatic disease or die
of the disease as they have non-lethal PC(5)”
Comment: I do not think reference 5 is appropriate here. That paper refers to a
Swedish analysis of the impact of PSA screening in Sweden on the preoperative
age and the risk of dying after a RP. A reference to SPCG-4 and PIVOT would
be more appropriate.
10. Line: “The survival benefit of RPs compared with watchful waiting in terms of
absolute reduction of PC death has been estimated to range between 0-25%
depending on the patient”6
Comment: Please rephrase. First, we don’t know how survival (time from
diagnosis/RP) to death is affected by RP compared to WW. We know that RP
“reduce the risk of prostate cancer specific mortality compared to WW”.
Secondly, he benefit, i.e. the reduction in risk of PCa death, of RP compared to
WW depends on the tumor characteristics – not “the patient”
11. Line: ”The only RCT evidence for a reduction in mortality was the SPCG-4
trial(7). Comment: It should be underlined that it was PCa-specific mortality.
12. Line: "However, as far as we know, the post-RP series are US based only". Comment: Is that a problem? If so, please underline why that’s important.

13. I want to congratulate the authors for their honest reporting of the PSM rates. The specific discussion about the PSM rates is relevant but lack one important factor – learning curve and low volume. The number of RPs per institution is low in 10-year time-span (although expected) in this series.

14. I think it is potential problem that 19.5% of the RPs performed in the time-span were excluded. Although that might be real-life reality, it has a major impact of the validity of the data. I think this should be commented in the Discussion section. Also, why exclude patients with skin cancer?

15. The title says: a case for a strong impact of PNI and PSAdt. Comment: Do the authors think that they have proved that here? Again, I think the authors should think a bit about how these results are translated into layman’s terms. For example, what the authors have shown is that the adjusted PSAdt of 3-8,9 months is associated with a hazard rate of 13.7 compared to patients with PSAdt of >15 months for the event PCa death, however, the HR lies somewhere in-between 1,5 and 124 (!!!).

   I think the title should be toned down a bit. This series represent a meticulous and important analysis of number of Norwegian patients but the validity of the data is low due to the statistical issues mentioned above.

Thank you.

Andreas Røder

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests