Author's response to reviews

Title: Importance and determinants of Gleason score understaging on biopsy sample of prostate cancer in a population-based study.

Authors:

Elisabetta Rapiti (elisabetta.rapiti@unige.ch)
Robin Schaffar (robin.schaffar@unige.ch)
Christophe Iselin (christophe.iselin@hcuge.ch)
Raymond Miralbell (raymond.miralbell@hcuge.ch)
Marie-Françoise Pelte (marie-francoise.pelte@hcuge.ch)
Damien Weber (damien.weber@hcuge.ch)
Roberto Zanetti (roberto.zanetti@cpo.it)
Isabelle Neyroud-Caspar (isabelle.neyroud-caspar@unige.ch)
Christine Bouchardy (christine.bouchardymagnin@unige.ch)

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Answers to the Editor and the reviewers

We thank the Editor and the reviewers for their very helpful comments which have all been considered in the revised manuscript. Please refer to the highlighted version of the manuscript.

Editorial comment.

1. Ethical Approval/Permissions

Can you please include a statement in the methods to clarify whether you obtained ethical approval for your study to use this data for publication purposes. Alternatively, can you please detail whether you required special permissions to use data from the Geneva Cancer Registry. Even if ethics approval is not required by a specific committee, the article should include a clear statement of this fact and the reasons why ethical approval is not required.

The Geneva Cancer Registry has general registry approval by the the Federal Commission of experts on professional secrecy related to medical research (Commission d’experts pour le secret professionnel en matière de recherche médical). This approval permits the collection of data of cancer illnesses throughout Switzerland and the use of data for research purposes. The patient’s data are kept strictly confidential in accordance with the requirements of the Data Protection Act. We added this information in the method section (page 6, line 20):

“All data analysis was conducted at the Geneva Cancer registry. The Registry has a general authorization, provided by the Federal Commission of experts on professional secrecy related to medical research, to collect nominative data for
research purposes on cancer in the general population.”

Reviewer 1

Reviewer’s report:
Well written article. Good grammar. No errors.
This manuscript does provide important population based data.
In my opinion, this article adds the body of literature supporting the performance of multiple biopsy cores to try and avoid understaging of prostate cancer. The more biopsies done, the more concordance there is with RRP staging.
The article does provide good population based data but the data, findings, conclusions are not unique.

We thank the reviewer for his comments. We have highlighted in the paper the salient point that an increased number of biopsy cores is associated with an increased concordance with the prostatectomy staging. We have in the discussion highlighted the other relevant body of work to which he refers.

Reviewer 2

Reviewer’s report:
In this interesting article by Rapiti et al entitled Importance and determinants of Gleason score understaging on biopsy sample of prostate cancer in a population-based study. The authors confirm previous literature that there is a modest concordance of biopsy Gleason score (grade) with prostatectomy Gleason score (grade) ~ 0.62 (67% exactly matching), then 26% were noted to have increase Gleason score on prostatectomy. Though the above is not novel, the authors further dive into their data and report that the discordance is related to age, number of biopsy cores, stage and time to prostatectomy. Explanation for age as a factor is ok, whereas explanations for other factors are quite good. In particular, it is fascinating how the discordance decreases with the number of biopsies obtained. I think this is quite relevant especially since the EUA has recently reduced the number of cores they recommend from 10 to 8. The goal of the biopsy is to obtain as much accurate information to make clinical decisions. Though there is a small risk associated with added number of biopsy cores it may be well worth it if the biopsy provides critical information especially in the 26% of patients with increased grade on prostatectomy. In fact I think this argument should be a bigger focus of the manuscript. Overall this is a well written, well laid out manuscript that is easy to follow and that adds something new to the literature. If corroborated, then perhaps the recommended number of cores to obtain will increase to at least 10. Below is a point-by-point critique of the manuscript.

TITLE: Perhaps through the text understaging should be converted to undergrading.

According to the reviewer’s suggestion we have changed the word understaging
into undergrading in the title and throughout the text.

ABSTRACT: First sentence in Methods is a little awkward otherwise no issues.

We changed the methods section of the abstract as follows:

“Methods: We considered for this study all 371 prostate cancer patients recorded at the Geneva Cancer Registry diagnosed from 2004 to 2006 who underwent a radical prostatectomy. We used the kappa statistic to evaluate the Gleason score concordance from biopsy and prostatectomy specimens. Logistic regression was used to determine the parameters that predict the undergrading of the Gleason score in prostate biopsies.”

INTRODUCTION: Nice introduction. It lays the groundwork for the study. Perhaps even mention how EUA has recommended reducing the number of biopsy cores.

The paragraph describing the factors associated with a lack of concordance between the biopsy and prostatectomy Gleason scores has been modified as follows (page 4, line 17):

“Several factors can influence the likelihood that the biopsy GS underestimates the prostatectomy score, including the PSA level, the level of pathologist expertise, the patient’s age, the results of the digital rectal examination, the prostate gland volume, the percentage of cancer cells in the biopsy sample and the number of biopsies obtained [5,7,9-11]. With reference to the last issue, it is worth mentioning that the European Association of Urologists (EAU) in 2008 recommended obtaining at least 10 cores during the biopsy [12], while in the most recent guidelines reduced this number to eight. [13].”

METHODS:
Please state that your local review board approved the study. Did it?

The Geneva Cancer Registry has general registry approval by the Swiss Federal Commission of Experts for professional secrecy in medical research (Commission d’experts pour le secret professionnel en matière de recherche médical). This approval permits the collection of data of cancer illnesses throughout Switzerland and the use of data for research purposes. The patient’s data are kept strictly confidential in accordance with the requirements of the Data Protection Act. We added this information in the method section (page 6, line 20):

“All data analysis was conducted at the Geneva Cancer registry. The Registry has general registry approval by the Swiss Federal Commission of Experts for professional secrecy in medical research (Commission d’experts pour le secret professionnel en matière de recherche médical). This approval permits cancer data collection and its use for research purposes.”

As authors state in discussion as a limitation, the same pathologist did not interpret everything. Thus one would anticipate from inter-observer variability.
We added in the Methods section (page 5, line 20):

“Different laboratories, from both the public and the private sector, examine biopsy and prostatectomy specimens in Geneva.”

RESULTS:
There is a good range of biopsy cores obtained in the face of EUA recommending 10 then 8 cores. Reasons for this?
The period under study covers the years 2004-2006, when the EUA recommendations in place were those published in 2001, where no suggestion on the number of biopsy cores was given (Aus G et al., EAU guidelines on prostate cancer. European Urology 2001; 40:97-101), and then those of 2005 that stated: “A minimum of 6-10 systemic, laterally directed, cores are recommended, eventually with more cores in larger glands (grade B recommendation)” (Aus G, et al. EAU guidelines on prostate cancer. European Urology 2005; 48:546-551.

Change the wording grade to Gleason score throughout the text.
Done.
The OR (multivariate) for age and delay, though significant, are quite minimal thus the significance loses significance.
The ORs for age and delay between procedures are estimated by unity of change of these two variables. This means that for age an OR of 1.04 translates in a 4% increase in probability of undergrading for each extra year of age. For delay between the 2 procedures an OR of 1.01 means an increase of 1% in the risk of undergrading for each extra day of delay between the biopsy and the prostatectomy. The p-values for these 2 variables are significant (p=0.038 for age, and p=0.018 for delay).
We rewrote the sentences in the results to better clarify this concept (page 8, line 8):

“In the multivariate analysis the variables independently associated with undergrading selected for the model were age, with a 4% increase by each extra year of age (OR: 1.04, 95% CI: 1.00-1.09; p= 0.038), clinical stage (OR: T3-T4 vs. T1-T2: 1.81, 95% CI: 1.06-3.10; p=0.030), number of cores (OR #9 cores vs. 10+: 1.93, 95% CI: 1.16-3.22; p= 0.011), and delay between biopsy and prostatectomy, with 1% increase by each extra day of delay between the 2 procedures (OR: 1.01, 95% CI: 1.00-1.01, p=0.018)”

REFERENCES:
No issues

TABLES:
Table 1 and 2 are quite similar. Is there a way to pictorially illustrate the concordance.

Please find below a graphic depiction of the concordance between biopsy and prostatectomy individual Gleason scores. We eliminated table 2 and left the results in the text. If the reviewer and the editors confirm that the graph below could substitute the table 1, the paper will end with one figure and one table.

Figure 1. Concordance between biopsy and prostatectomy individual Gleason scores.

Empty circles represent concordant scores between biopsy and prostatectomy; red filled circles represent discordant scores. The size is proportional to the number of cases falling in each combination.