Author's response to reviews

Title: MRS-guided HDR brachytherapy boost to the dominant intraprostatic lesion in high risk localised prostate cancer

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Version: 2 Date: 14 May 2010

Author's response to reviews: see over
Thank you very much for your comments. The summary of our response and corrections follows below.

Please also note that the affiliation of second author, Guy Godwin, was changed.

Kind regards,
Aleksandra Kazi

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**Reviewer's report**

**Title:** MRS-guided HDR brachytherapy boost to the dominant intraprostatic lesion in high risk localised prostate cancer

**Version:** 1  **Date:** 8 January 2010

**Reviewer:** Juanita Crook

This manuscript is well written and provides useful information on an important and very current issue: dose escalation to the dominant intra-prostatic lesion where tumor bulk and potential radio-resistance demand a higher dose for cure than can be safely given to the entire prostate. I have some specific suggestions for clarification and additional information which should be incorporated to enhance the article and make it more useful for those beginning a similar program. I have no compulsory major revisions, only minor revisions.

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**Page 3, Materials and Methods, paragraph 2:** Please add information on the prostate volume (this influences critical organ doses)

Information added – prostate volume was 63cm$^3$.

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**Please add information on the number of diagnostic biopsies which were obtained. Often “sextant” biopsies consist of 12 cores with 2 per sextant which provides a more thorough sampling of the gland. It sounds like only 3 were obtained for this case.**

Explanation added in the “Material and Methods” section:

“Six specimens of tissue were obtained with transrectal ultrasound sextant (TRUS) biopsy, each consisting of thin fragments of tissue measuring 12-18mm in length. The biopsy revealed adenocarcinoma of the prostate in the three cores on the right side and none in the three cores on the left side of the prostate, with 100%, 70% and 30% of core involvement in the right superior, mid and inferior cores, respectively.”

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**It is stated that the patient had “clinical T3a” disease. Was there suggestion on TRUS or MRI of extracapsular extension or was this purely on the basis of DRE?**

The stage was based on the DRE and the MRI. It was also consistent with the biopsy results showing all cores from one side extensively replaced by prostate adenocarcinoma Gleason score 7. Statement in the manuscript:

“The prostate specific antigen (PSA) at diagnosis was 5.3 ng/ml and the clinical stage from digital rectal examination and the MRI was T3a according to AJCC-TNM[13].”

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**Page 4, paragraph 3:** The voxel size is quite large (10x10x10 mm = 1 cc). This reviewer is accustomed to using voxels which are 7 mm per side for volume of 0.34 cc. Was there a reason that such a large voxel size had to be used?

Statement added:

“With further optimisation of our MRS technique we were able to decrease the voxel size to 7x7x7mm$^3$ while keeping a similar signal to noise ratio. However all patients scanned using the smaller voxel size had multiple dominant lesions in the prostate, thus could not be used for this study as the dose escalation to the dominant lesions would not be practical.”
We were not able to rescan that particular patient, as he was already administered androgen deprivation therapy (ADT), and it is known that with time on the ADT the MRS-detected metabolite signal decreases until reaching noise level.

Paragraph 4, last line: “MRS doesn’t have sufficient resolution”. This relates partially to the voxel size and a comment should be made to this effect to clarify for the reader.

Statement added: “The DIL was subsequently delineated according to this region of hypointensity on MRI, as MRS didn’t have sufficient resolution for accurate delineation, even if the small voxel size of 7x7x7mm$^3$ was used. The resolution of MRS could be improved if the voxel size was decreased, however it would also mean decreasing the MRS signal strength. Further progress in signal acquisition and technology is necessary to improve the signal-to-noise ratio, thus allowing a smaller MRS voxel size.”

Page 4, last line: If the prostate dose is 7.5 Gy and the SIB dose to the DIL is 7.5 Gy, why does this state that 20 Gy was given to the DIL? Also what was the margin on the MR-delineated DIL. 20 Gy to the GTV DIL and 15 Gy (7.5 + 7.5) to the PTV DIL would make sense but this should be clarified.

The value should have been 15Gy and was corrected.

Page 5: please add a reference for the ratio of clonogens being 90:10 for the DIL compared to the prostate.

Reference was added.

Page 6, External Beam Plan: Please provide more details such as the beam arrangement, conformal vs. IMRT, prescription point or isodose, etc.

Added in description of Plan A:
“conformal plan utilizing 5 10MV photon beams with corresponding gantry angles of 0°, 54°, 83°, 253° and 282°

prescription dose: 74 Gy delivered in 37 fractions
for the PTV$_{EBRT}$: V95 to be equal 100%; however in this case, due to rectum DVH being close to tolerance and the particular rectal filling, the radiation oncologist accepted the plan with V95 of 98% for the PTV$_{EBRT}$”

It would be helpful to include a distribution for all 3 plans.
The dose distributions for representative transverse images were included (Figures 2A, 2B and 2C).

Page 7, Discussion: Please add a comment concerning the contribution of MRS to this treatment plan. It seems it only confirmed what was already known from biopsies and anatomic MRI. This related back to the importance of adequate sampling of the gland at the time of biopsy to minimize the risk of missing a 2nd potentially important lesion which would preclude using this approach.

Added:
In a certain group of patients, where multiple DILs are present, the delivery of a boost dose to the dominant lesions can be impractical. Performing MRS was important to establish that a second potentially important lesion doesn’t exist as it could preclude delivery of the boost dose. Thus MRS was not only confirming the results of biopsy and MRI.

Table 3: Why is the V100 so low for an external beam plan?
Because of the planning aim being defined as V95 = 100% for the PTV$_{EBRT}$ (i.e. 100% of PTV$_{EBRT}$ receiving 95% of 74 Gy, that is 70.3Gy). This information has been added as described above.
Table 4: Misplaced decimal in the 1st column for the V125.
It was corrected.

Also, why are the SIB HDR D100 and D90 so high? This relates back to the question concerning page 4, plan C, intended dose 7.5 Gy + 7.5 Gy to DIL.
The table 4 was corrected (unfortunately we have previously attached an older version of the table).
Table 5 was checked and is correct.

With these additions and clarifications, I think the reader will find this a very informative and interesting article.

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**
I have no competing interests.
Reviewer's report
Title: MRS-guided HDR brachytherapy boost to the dominant intraprostatic lesion in high risk localised prostate cancer
Version: 1 Date: 8 February 2010
Reviewer: Charles Rosser
Reviewer's report:
This is an interesting article from Kazi et al. reporting on the use of MRS in treatment planning for patients undergoing focal radiation therapy for prostate cancer. The article is well written and clearly depicts in one patient how MRS may be incorporated into radiation therapy treatment planning.
Below is a point by point critique of the article.

Abstract/Background
No concerns

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Material and Methods

Only sextant biopsy? Typical guidelines usually recommend more sampling of the prostate.
Unfortunately the sextant biopsy of prostate was the standard approach at the Townsville Hospital at the time of the study. A statement explaining that was added to the “Material and Methods” section, “Patient” subsection.

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1.5 T MRI with body coil not endorectal coil used. Some suggest images and staging capability is better with 3T MRI.
We agree with that, however again we had only access to the 1.5T MRI scanner. We have found the signal-to-noise ratio for the MRS data collected using that scanner to be acceptable, provided a careful, manual shimming of the magnetic field was performed.
Added:
“We have found that when using the 1.5T scanner and no endorectal coil, the manual shimming was crucial to obtaining spectra with acceptable signal-to-noise ratio.”

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The MRI was performed without contrast (i.e., no DCE?)
The MRI was performed without contrast (it was dedicated to the image fusion with the CT images for radiotherapy planning).
Statement extended:
“MR images were obtained with a 1.5T clinical scanner (Magnetom Symphony, Siemens, Erlangen, Germany), without contrast.”

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Patient is high risk. Did he get ADT?
Yes. Statement added:
“external beam radiation therapy (EBRT) combined with androgen deprivation therapy (ADT) starting 6months prior to the start of EBRT and continuing for two years after completion of EBRT”

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Is a patient with T3a prostate cancer, the best candidate for focal therapy?
Added:
“T3a patient is not the ideal candidate for focal therapy [27]. However in this case we were able to reliably establish the location of the lesion within prostate and the prostatic volume outside of the DIL still received dose of 60Gy of the EBRT and 7.5Gy of the HDR brachytherapy for the SIB plan.”
Results

How would you monitor success? Nice addition of dose volume parameters (standard now for brachytherapy).

Added in discussion:
“The success of treatment employing the selective boost to the dominant lesion could be monitored with regular PSA tests. Follow-up MRS to detect any remaining choline levels could also be performed; however we’re not aware of studies investigating the optimal timing of prostate MRS for radiotherapy follow-up. Repeated MRS investigations could be done, however such an approach would not be cost-efficient. Another option would be performing MRS when indicated by increasing PSA. The saturation biopsy could also be employed in this case.”

Figure 1 looks nice. Can you also include just the MRI image so that readers can see if a mass is present.

The MRI image was added as figure 1B.

Do you have a follow-up MRS that does not illustrate the choline activity?

We have a follow-up MRS at 6 months post-EBRT, which doesn’t show any activity (no choline and no citrate). However the patient is still on the androgen deprivation therapy, thus it is unclear at this stage if the lack of activity on the MRS is due to the success of treatment or due to the effect of androgen deprivation therapy (which is known for suppressing the metabolite levels on MRS). We have not included this data in the manuscript, but please let us know if you would prefer us to do so.

Discussion

Discuss your next step. Is MRS enough for evaluation? Is there a role for saturation biopsy? Can this treatment be repeated if tumor recurs ‘out of field’?

Added in Discussion (as also mentioned above):
“The success of treatment employing the selective boost to the dominant lesion could be monitored with regular PSA tests. Follow-up MRS to detect any remaining choline levels could also be performed; however we’re not aware of studies investigating the optimal timing of prostate MRS for radiotherapy follow-up. Repeated MRS investigations could be done, however such an approach would not be cost-efficient. Another option would be performing MRS when indicated by increasing PSA. The saturation biopsy could also be employed in this case.

However even if a recurrence of tumour in another location within the prostate was detected, retreatment would be difficult because of the doses already delivered with the SIB plan.”

Conclusion
No concerns

References/Tables/Figures
See above

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have no competing interests.