Author's response to reviews

Title: Recent advances in the diagnosis and treatment of bladder cancer

Authors:

Grace Cheung (dr.grace.cheung@gmail.com)
Arun Sahai (arun.sahai@gstt.nhs.uk)
Michele Billia (michele.billia@gstt.nhs.uk)
Prokar Dasgupta (prokarurol@gmail.com)
Muhammad S Khan (Shamim.khan@gstt.nhs.uk)

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Author's response to reviews: see over
Dear Editors,

We are very grateful to the peer reviewers’ for their time in extensively reviewing our draft manuscript. Their comments are important and valid and we have therefore taken into them account when revising our manuscript.

We hope this new manuscript meets your expectations and that you find it satisfactory for publication.

Please find below our responses to the reviewers.

Best wishes

Grace Cheung

Reviewer's report
Title: Recent Advances in the Treatment of Bladder Cancer
Version: 1 Date: 11 July 2012
Reviewer: Peter Black
Reviewer's report:

1. The abstract is a list of facts about bladder cancer – it needs some context. The title is the only hint of what the authors want to do here.

   Our abstract has been amended.

2. The Introduction is disjointed – it is a list of facts about bladder cancer that lead to the statement that the authors want to summarize recent advances. It needs to set the stage better for why this is a timely review and what the main issues in bladder cancer are. Also, why not include Cis with NMIBC? And what about BCG refractory T1 disease for cystectomy?

   Our introduction has been amended as per suggestion.

3. The discussion of each advance should include some sort of summary statement of where we stand now and what potential next steps might be. This “synthesis” is the key to a good review. For example, what do we do with the apparent contradiction with PDD that it detects more tumors but may not improve outcomes? The authors could mention here also the fact that these studies were done without post-TURB intravesical chemotherapy, which may further diminish the benefit of PDD. Also how do PDD and NBI compare? Some pros and cons of each would be helpful.

   We have included comparison of PDD vs NBI.

4. For the markers, there is little new about either NMP22 or Urovysion – except the article from Kamat on Urovysion for BCG response. Has anything in Table 1 changed over the past 5 years? Also, the authors cannot simply cite another review of markers as a sole reference for their own review. Again little synthesis here – how should we use these markers? Is there anything new out there? Why are we not more successful in adoption of markers?

   We have amended this section as per suggestion.
5. The passage on dose reduction of BCG seems out of place. There are several “tricks” for reducing toxicity, including use of antibiotics and isoniazid, so why highlight dose reduction only? It is also a bit out of place coming right before a description of electromotive MMC, as if electromotive MMC was designed to improve BCG tolerability. Hyperthermia and EMDA are both promising – is it being adopted anywhere? Is it on trial only? Has it been approved for routine use anywhere? If not, why not, and what is the next step?

We have removed section on dose reduction of BCG and include use of EMDA.

6. For intravesical gemcitabine, SWOG is just finishing a trial for single does post-op – so this should not be discounted. The authors should comment a little more about trials that have been done for adjuvant intravesical gemcitabine – here they give the context (promising but limited data), but not the data.

Data on intravesical gemcitabine included and also SWOG trial data.

7. The RCT on robotic cystectomy by Nix has been criticised for very low numbers (inadequate power) – this should be mentioned in a review like this. Since one of the authors is a key member of the IRCC, the authors need to be careful about providing a balanced review of robotic cystectomy. “Motivated robotic surgeons” seems a bit embellished. On the other hand, this is a rapidly developing area of bladder cancer treatment and probably deserves more attention than the authors are giving it. Any idea, for example, on how widely RARC is being adopted in North America and Europe? The part about prospective trials that is currently in the Conclusions belongs in this section.

Removed “motivated” section and included nos of RARC performed and ongoing trials.

8. The section on bladder preservation reflects the usual urologist bias (as does the last sentence of the paper) – especially in the UK, from where the authors hail, radiation is not just for those declining or deemed unfit for surgery! The paper by James et al is significant and deserves more attention. Why should this not convince us in North America to do a lot more bladder preservation (as is already done in the UK)? If the authors consider chemorads inferior, they need to make that case, especially in light of the James paper.

We do not believe chemorad to be inferior and therefore have re-worded our abstract, intro, bladder preservation and conclusions sections accordingly.

9. The authors comment in the conclusion that mortality is declining from bladder cancer – this does not come out anywhere else in the text and is not referenced. This would be truly new! Otherwise the Conclusions reads a bit like a shopping list.

Mortality sentence removed. Conclusions modified

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10. A couple of things come to mind that are not addressed:

1. Work on identifying markers that predict response to neoadjuvant chemotherapy; eg. Dan Theodorescu’s Coxen model
2. German and US trials on value of extended pelvic lymph node dissection
3. Update on trials for adjuvant chemo – there have been several published recently (at least as abstracts)

These areas have not been included as several other areas have been expanded and the authors would like to keep within an acceptable word count. As the
readership is mostly medical, rather than surgical, we have not included a section on PLND in this paper.

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
Reviewer's report
Title: Recent Advances in the Treatment of Bladder Cancer
Version: 1 Date: 7 June 2012
Reviewer: SHAHROKH Shariat
Reviewer's report:
- Major Compulsory Revisions
  1) Urinary markers (Second paragraph): The discussion of FISH is too one-sided. Downsides should be discussed including the high false-positive rate and the high expense (mentioned in the table). The readership, which is largely non-urologists, would currently come away thinking that FISH should be a clear standard-of-care.
  We have amended this section as per suggestion.
  2) Non-muscle invasive bladder cancer (first paragraph. Fourth sentence): After this sentence, it is important to note that single-dose perioperative intravesical chemotherapy as monotherapy is only appropriate in patients with tumors at low risk of recurrence and progression (AUA guidelines: Hall et al, 2007 and EAU Guidelines: Babjuk et al, 2011). For patients with greater than low-risk UCB, additional intravesical installations are recommended.
  We have amended this section and referred to EAU guidelines.
  3) Diagnosis (Second paragraph. ): Reference #4 is a prospective randomized trial comparing BLC and WLC. As stated, recurrence rates were lower at 1 and 2 years in the BLC group. Reference #5 is a RCT that did not show a difference between BLC and WLC in terms of progression-free or recurrence-free survival. Would specify these as the “outcomes” that were not improved. I would also include a recent study presented at the AUA 2012 from H.B. Grossman et al.: Abstract 1668: Long-term clinical benefit of hexaminolevulinate enabled fluorescence cystoscopy (http://www.aua2012.org/abstracts/process.cfm?ID=H.+Barton%2FGrossman&searchType=presenter&This is another prospective, randomized study that shows improved RFS (16.4 vs. 9.6 months; p-value < 0.04) in patients followed with BLC. Median f/u was >53 months. I would argue that the improved RFS seen in two prospective studies are highly meaningful outcomes.
  Amended – HAL meta-analysis included which shows more positive overall results and therefore abstract not included.
  4) BCG/EMDA Mitomycin C: Discussion of BCG/EMDA should provide an explanation of what the actual treatment entails and what the rationale is behind it. For example, citation #25 authors conclude that “BCG-induced inflammation might increase the permeability of the bladder mucosa such that mitomycin can reach the target tissue more easily and exert its anticancer effect.”
  We have amended as per suggestion.
  5) Hyperthermic MMC (last 2 sentences): should add that the systematic review was limited by a small number of randomized trials. Also, the last sentence is a
conclusion of the authors of citation #29 and should be stated as such. That hyperthermic-MMC “may become standard therapy for high-risk patients” is highly speculative.

**We have amended as per suggestion.**

6) Intravesical Gemcitabine: This section is poorly described and doesn’t provide anything to help the reader. The randomized trials in the Cochrane review are comprised of very heterogeneous patient populations. Consider the abstract from AUA 2012 from Skinner et al. 1666: SWOG S0353: Phase II Trial of Intravesical Gemcitabine in Patients with Non-Muscle Invasive Bladder Cancer Who Recurred Following at Least Two Prior Courses of BCG. http://www.aua2012.org/abstracts/process.cfm?ID=Eila%2FSkinner&searchType=presenter&searchKey=Patients who had failed 2 prior BCG treatments were given 6 weekly Gemcitabine doses and then monthly maintenance x 12 months. At one year, only 28% of evaluable patients had a durable response.

**We have amended this section and included abstract.**

- **Minor Essential Revisions**
  1) Introduction (fourth sentence): should also include high-grade recurrent T1 UCB and BCG-refractory T1 UCB as groups that should undergo RC.

**We have amended this section as per suggestion.**

2) Urinary markers (Third paragraph. Last sentence): “Low threshold for performing a cystoscopy” should be better clarified. Would suggest using the actual numbers: “For physicians who would perform a cystoscopy if the risk for recurrence was 5% or if the risk of progression was 1%, the use of NMP22 did not aid in clinical decision-making.”

**We have amended this section as per suggestion.**

3) Muscle-invasive bladder cancer (third paragraph. Last sentence): Expression “fewer degrees of freedom” isn’t clear in this context. Please clarify your intended point here.

**We have clarified this sentence as per suggestion.**

- **Discretionary Revisions**
  1) Introduction (second sentence): may be more accurate to say….i.e. NMIBC, which has a high risk of recurrence, and a variable risk of progression.

**We have amended this section as per suggestion.**


**We have amended this section as per suggestion.**

3) Muscle-invasive bladder cancer (paragraph discussing DaVinci): After the fourth, a sentence about comparative complications between RARC and ORC should be added. Ng et al., Eur Urol, 2010 demonstrated a lower 30 and 90 day complication rate comparing RARC and ORC.

**We have amended this section as per suggestion.**

"Minor issues not for publication:"

1) Abstract: (First paragraph. First sentence) Would use an alternative term to “investigations” such as “tools.”

**We have amended as per suggestion.**

2) Diagnosis: (first paragraph. Third sentence) add the word “and.” As in “…assessed with HAL, and in the initial follow-up of patients with CIS or
multifocal tumors.

We have amended as per suggestion.

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:
Consultant to Ferring Pharmaceuticals