Reviewer’s report

**Title:** Recent Advances in the Treatment of Bladder Cancer

**Version:** 1  **Date:** 7 June 2012

**Reviewer:** SHAHROKH Shariat

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- 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.

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.

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=pre). 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.

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.”

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.
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. 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.

- 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.

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.”

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.

- 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.


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.

"Minor issues not for publication:"

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

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.

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