**Peer Review File**

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**Reviewer A**

The study includes rather few patients, yet as a retrospective pilot investigation with the intent to be hypothesis generating, the amount of study subjects does suffice.

**Thank you very much for your insightful comments. We agree that this study is only meant to be hypothesis generating that may shed light on non-BCG alternatives for NMIBC.**

Still there are some missing data which would need presentation.

1. During the same period, how many patients at your institution actually received BCG? And what were the outcomes for that subgroup?

**Reply 1: During the study period, 9 patients received BCG therapy after being referred to another Banner Health facility. Our clinical practice is to offer all patients a referral to obtain BCG therapy elsewhere but unfortunately many are unable to drive to our external facility located 100 miles away (Gilbert, AZ). We did not include these patients in the current study since they chose to follow elsewhere. We will clarify this in the text.**

**Change in the text: During the study period, there was a shortage of BCG supply and therefore none of the patients included in the analysis received BCG. (page 4, line 32)**

2. During the same period, how many patients at your institution went to direct cystectomy?

**Reply 2: There were 14 patients who went directly to radical cystectomy after clinical consultation, all of whom possessed HG T1 disease. These were not included in the current study.**

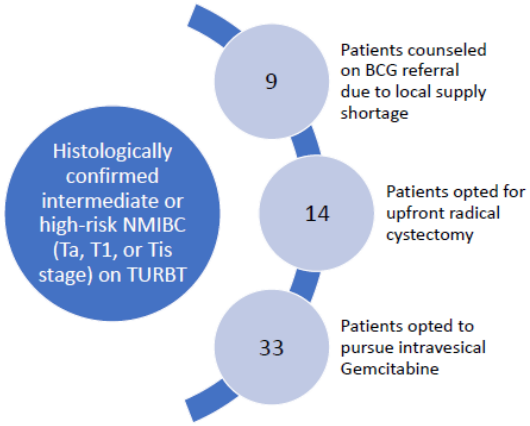
Request (i): The authors need to display the full picture with all patients having intermediate or high grade bladder cancer being treated at the institution.
The article needs to display those two subgroups in the same manner, in all aspects, as the Gemcitabin-group is displayed.

**Reply: Thank you for the comment. Since we did not intend to have a comparative study, we did not include the patients who received intravesical BCG elsewhere.**

Request (ii): A figure including all three patient-groups mentioned above, bening displayed in a flow scheme needs to be prepared and included in next submission.

**Reply: Thank you for the comment. Although we did not include any patients who received intravesical BCG in our analysis, we have prepared a flow scheme detailing our treatment counseling management in a flow scheme to**

**be entered as supplementary figure 1.**




3. From the cT1-group being treated with Gemcitabine I want to have following information:
(a) Size of the tumors?
(b) Any concomitant CIS or not, specifically in the cT1 study subjects? [table 1 gives some information concomitant CIS and LVI, but I cannot figure out if these ominous markers are related specifically to the cT1-subgroup or not?]
Request:
(i) Please expand information on the cT1-group.
**Reply 3: Very good comments to present. The average size of tumors in cT1 group was 2.3cm (0.5cm – 6.5cm). The distribution of CIS was added to table 1 (4 HGT1 patients had CIS and 2 HGT1 patients had LVI)**
**Change in the text: We added the information to page 5, line 32 and table 1 as kindly requested.**

(ii) I would like the authors add in the DISCUSSION expand on some thoughts related to letting cT1-patients with concomitant CIS and/or LVI not receive standard BCG-treatment and in select cases; not proceeding to direct cystectomy.
**Reply: Thank you for the very important comment. We agreed that patients with concomitant CIS and/or LVI would be better served with standard intravesical BCG or upfront radical cystectomy, if willing or fit to proceed. We extensively discussed these options with patients who presented with cT1 disease. Those who were included in the current study desired to preserve the bladder as the first line treatment or were unfit for cystectomy.**
**Change in the text: We added the following to discussion section, page 7, line 37 based on the reviewer's knowledgeable comments.**
**"It is noteworthy that patients who have adverse risk factors, including lamina propria invasion, large tumor size, concomitant CIS, presence of LVI are associated with cancer progression and worse survival (26). In the absence of adequate intravesical therapy, radical cystectomy should be offered for those willing or fit for surgery."**

4. On page 5 under DISEASE OUTCOMES, we read:
"A total of 12 recurrences occurred over the study period. The 3-month CR was 84.8% (28/33). Four recurrences were high-grade NMIBC. There was one progression to invasive disease treated with cystectomy".
Request: Please explain; What were the specific characteristics of the four HG-patients who experienced recurrence? Were there any early signs predicting recurrence for them?
I think this needs to be displayed clearly.
**Reply 4: Thank you for your detailed question. All four patients with high-grade recurrence had HG multifocal disease at initial presentation. Three out of four (75%) had early recurrence at 3 months. Half of them had concomitant CIS. These findings go very well with reviewer's previous thoughtful comment on emphasizing the role of early cystectomy for these high-risk cases.**
**Change in the text: We added the details of the four recurrences to the Results. Page 5, line 38.**

**Reviewer B**
Overall small, good study in area where much investigation is still needed.

I only have one minor remark: you could mention somewhere that other recent alternatives have been explored recently such as gem/docetaxel combination and nadofaragene firadenovec.
Despite the limited sample this is an area of ongoing debate and investigation. Therefore, this can be a nice addition to the literature.

**Reply: Thank you for the kind comments. We agree that due to the limited options in NMIBC, our study could add data for patients unable to receive BCG (either from supply shortage or intolerance).**

**Change in the text: We have added the following discussion to page 7, line 15.**
**"Recently, McElree et al. reported a series of 107 patients with high risk NMIBC receiving sequential gemcitabine and docetaxel (23). The RFS was 89%, 85% and 82% at 6, 12 and 24 months, respectively. Adding docetaxel seemed to improve the RFS when compared to gemcitabine alone. Nadofaragene firadenovec (a novel agent delivering interferon alfa-2b cDNA into the bladder epithelium) has been recently approved by the FDA based on a multicenter RCT for BCG-unresponsive NMIBC (24). Complete response within 3 months of the first dose was seen in 55 (53.4%) of 103 patients with CIS (with or without a high-grade Ta or T1 tumor). More prospective studies are needed to compare different agents and regimens in high risk NMIBC."**

**Reviewer C**

The authors present a single institution, non-comparative cohort series of patients with HG NMIBC who received intravesical gemcitabine with acceptable oncologic efficacy and safety. Some comments:

1. The use of intravesical gemcitabine as first line agent for HG NMIBC is neither new or novel. This has been shown to be effective and well tolerated in a number of prior reports including larger and prospective series.

**Reply 1: Thank you for the comment. Although gemcitabine has been reported to be effective as first line agent, this has been in sequential fashion with other agents such as docetaxel. Our report is novel in reporting single agent intravesical chemotherapy although we do acknowledge that BCG will remain the standard of care for high risk NMIBC when able to receive adequate administration.**

2. The proportion of patients who completed adequate maintenance therapy is small (roughly a third) which is not adequately explained in the paper.

**Reply 2: Excellent comment. During the late period of study, we encountered difficulties in scheduling patients for maintenance therapy at our cancer center due to the rise of the COVID-19 pandemic.**

**Change in text: We have added this explanation in page 6 line 6.**

3. Given the relatively small number of patients included that were BCG exposed it is not clear why these are included in the series instead of just reporting on the BCG naive cohort.

**Reply 3: Thank you for the comment. We initially included only BCG naïve patients which showed slightly better recurrence outcomes but one of our esteemed senior authors recommended we include the few BCG exposed patients for more accurate reporting of our data.**

4. In the absence of BCG it is logical to use alternative agents as we as done here, but the fundamental question is really whether this should be a substitute for BCG and this study cannot address that query.

fundamentally un-interesting as it adds very little to our knowledge given the small sample size and non-comparative nature of the study.

**Reply 4: Thank you for the comment. We acknowledge the study is not meant to justify replacing BCG as the standard of care. Only a randomized controlled trial can do that; but unfortunately, it is unlikely to ever happen for ethical reasons. We did not seek to fundamentally change the treatment for NMBIC but merely to report our contemporary outcomes during the current nationwide shortage of BCG supply. It is our hope that the manufacturing of BCG can eventually meet the demand for all patients with HG NMIBC while further research into first-line BCG alternatives can continue in a collaborative fashion.**