AUTHOR'S REPLY

Reply to: Wojciech Krajewski, Sławomir Poletajew. The TaHG bladder cancer – the devil is as black as he is painted. Cent European J Urol. 2019; 72: 76-77.

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We thank the authors for raising pertinent questions regarding our work and particularly the topic of second (re) TURBT. We would like to put into perspective the observations made by the authors of the letter.

While enumerating the reasons why second TURBT group did not show statistically significant improvement in recurrence free survival they point out: 1."the population was small, (only 43/112 TaHG patients underwent reTURBT) and therefore the number of events was low. As only a minority of TaHG patients underwent reTURBT, this raises questions about the indications for the procedure in selected cases". We agree that the population studied was small as the study was about a focused pTaHG group, and it is difficult even for a high-volume center to accumulate substantially larger experience in pTaHG tumors over a decade. This statement is corroborated by the fact that there is a paucity of studies on this focused group. Most authors combine their data with the rest of the pT1 group for the same reason, resulting in lack of focus on the pTaHG group. The second part of statement raises question about the reasons why only 43 out of 112 patients were offered second TURBT. We did analyze this aspect and found two reasons for this: the minor one was patient compliance, as around 55 patients out of 112 were advised second TURBT but only 43 followed up for the same. The more important reason was that more than half i.e. 57/112 were not advised second TURBT. Despite ours being a referral academic center and the EAU guidelines recommending a second TURBT since 2006 for pTaHG tumors, there was a lack of consensus among various consultants regarding the need for second TURBT in the pTaHG group. To our surprise, this experience was not limited to our institution alone. We presented this study in the American Urology Association meeting held at San Francisco in 2018 and at the end of the presentation the chairman of the session (Dr. Ashish Kamath) asked the attending urologists to raise their hand if they would have offered second TURBT in patients with pTaHG lesions, and only a small minority raised their hands. Among the attendees present there was at least one serving member of the EAU guideline panel for non-muscle invasive urothelial cancer. This reflects that despite the EAU recommending a second TURBT from 2006 to 2016 (the study duration) there was little consensus among practicing urologists regarding the same and hence clinical practice has been variable worldwide, in our experience.

2. "Secondly, only a minor percentage of patients were given BCG maintenance, and some received only MMC. One of the advantages of reTURB is its positive effect on BCG efficacy. However, as widely proved, in high-risk patients BCG maintenance is obligatory to substantially reduce the risk of recurrence and progression". We would point out two important facts here. First, the definition of maintenance BCG varies between different authors. In our study, we defined and included only those who had received at least one year of maintenance BCG in this group, while patients who had received less than one year of maintenance BCG were classified under the induction BCG group. In their study, the authors have defined the maintenance BCG group as patients who received one intravesical BCG more than the induction group i.e. 7 intravesical BCG (6 for induction and 1 for maintenance) [1]. Such patients in our study would have been included in the induction BCG group, and this makes direct comparison problematic. Second, and more importantly, the prognostic classification of EORTC (which is the basis for the EAU guidelines) were based on the WHO 1973 histopathological classification of urothelial tumors (a position that the EAU guideline panel has maintained till the 2018 version of the guidelines) and hence a pTaG3 tumor, which is definitely an indication for intravesical BCG based on published data is not the same as a pTaHG lesion. In our experience, pTaHG is a more heterogenous group

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which includes previously classified G2 lesions (9 out of 14 such patients on reclassification were labelled HG lesions in our study, see Figure 1) [2]. This heterogeneity and variable aggressive biological potential has been shown by others as well [3]. So the question as to whether all patients classified as pTaHG lesion warrant intravesical BCG is yet to be answered. In an effort to incorporate the WHO 2004 classification for prognostication, the EAU guidelines have suggested accumulating long-term individual patient data and reporting it in time to event format. This point is best illustrated by reference 2 of their letter, where the outcomes of second TURBT are assessed on a group of patients who were classified based on the WHO 1973 classification [4].

3. Finally, the follow-up period was short. We do agree that the follow-up period of our study was short as we have mentioned this as one of the limitations of the study. Follow-up duration definitely impacts outcomes. We studied the authors' experience with second TURBT in pTaHG lesion with great interest [1, 5]. Here, we would only like to point out that one of the important variables affecting the discovery of residual tumor at the second TURBT is the center at which TURBT was done as has been shown by the combined EORTC database [6]. This would mean, until the time we have large multicenter trials assessing the utility of second TURBT in the pTaHG group, single centers can use it as a quality assessment tool for first TURBT and then selectively apply it as per their experience.

We agree with the authors that all these studies including ours do not present strong unbiased evidence which could lead to changes in clinical practice or impact existing guidelines. However, they do provide the scientific community with an evidence based hypothesis and ethical reasons to invest time and resources to study these issues in an unbiased manner through planned prospective multicenter studies so as to generate evidence and to which clinical practice can be aligned.

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