



# T1G3 bladder cancer, bacillus Calmette-Guerin and radical cystectomy: continued debate

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T1G3 bladder cancer is an unpredictable beast and remains a controversial topic within the urology community. The optimal treatment strategy is a hotly contested subject; in responders, maintenance intravesical instillations of bacillus Calmette-Guerin (BCG) and close endoscopic management offers adequate cancer control with a bladder sparing approach. However, in non-responders it delays and compromises oncological outcomes in a cohort better served by early radical cystectomy (RC). The stakes remain high; left untreated up to 64% of T1G3 will exhibit disease progression (1) and long term up to 34% of patients will die of bladder cancer with either treatment option. treatment (2). This delicate balance between over-treating potential BCG responders with a highly morbid surgical procedure compared to undertreating those likely to progress continues to confound urologists and patients. Soria's study on predictors of oncological outcome in BCG treated T1G3 patients undergoing RC published in August's issue of the *World Journal of Urology* revisits the debate (3).

Soria *et al.*'s retrospective multicentre study (23 centres) reports on oncologic outcomes and predictors for RC in patients initially treated with BCG for T1G3 (WHO 1973)/high grade (HG) (WHO 2004) bladder cancer (3). From a 2,451 strong cohort of T1G3/HG patients receiving BCG between 1991 and 2011, 509 (20.8%) underwent RC (4). The presence of carcinoma in situ (CIS), tumour size  $\geq 3$  cm, multifocal tumours, absence of muscle in first resection, presence of T1 in second resection and lack of maintenance

BCG were all significant predictors of RC. The presence of CIS and tumour size  $\geq 3$  cm at diagnosis were associated with the worst prognosis and shortest interval to RC.

A total of 226 (44%) patients progressed to muscle invasive disease prior to RC, 111 (22%) were upstaged after RC and 172 (34%) patients did not progress. Of the 337 patients that progressed, 153 (45%) had locally advanced T3/T4 and 72 (21%) had positive lymph nodes (N+). The presence of CIS, tumour size  $\geq 3$  cm and multiple tumours at diagnosis were all predictors of pathological upstaging to T3/4/N+ disease after RC. One hundred and thirteen (22%) patients died a cancer-related death, 76 (67%) of these exhibited progression prior to RC, 25 (22%) were upstaged after RC and 12 (11%) showed no progression. Time to cancer related death was shorter in the 27 (33%) patients with disease progression. Furthermore, those with recognized progression prior to RC had a shorter time to cancer death compared to those upstaged on post-cystectomy histology. CIS at cystectomy and T3/4 or N+ at cystectomy were associated with shorter disease specific survival.

The authors should be commended on their original approach to describing variables predicting for RC. Most literature on the subject focuses on variables related to disease progression and recurrence. However, in truth there is little fresh insight gained by focusing on risk factors for RC as these, unsurprisingly, mirror those associated with disease progression and recurrence. Current 2018 EAU

guidelines on non-muscle invasive bladder cancer (NMIBC) sub-stratify a group of high risk NMIBCs into the 'highest-risk' tumours for progression, based on a variety of multivariate analyses (5). This group includes T1G3/HG with concurrent CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, unusual histology such as micropapillary, plasmacytoid, sarcomatoid and lymphovascular invasion (LVI). For this subgroup, the EAU guidelines recommend early RC should be considered and for those unfit or unwilling BCG treatment should be offered instead. For patients receiving BCG, the EAU recommend consideration of RC in BCG treated patients that progress to muscle invasive disease, continue to have or develop CIS at three months and six months post BCG initiation, those that are intolerant to BCG side effects and those who continue to have G3T1/HG at three months. EAU also recommend upfront RC is considered in patients who recur with G3T1/HG more than a year post BCG treatment, at which point further BCG or RC should be considered. Given the recommendations for the 'highest risk' subgroup, it is not surprising that patients in the study with CIS and tumours  $\geq 3$  cm at diagnosis were more likely to receive RC earlier, as both are known to increase the risk of disease progression.

The early European Organization for Research and Treatment of Cancer (EORTC) risk calculators based on 2,596 NMIBC cancer patients did not include patients treated with BCG (6). However, the presence of CIS and tumour size  $\geq 3$  cm were both shown to worsen prognosis due to increased recurrence rates, additionally CIS increased the risk of progression, corroborating Soria *et al.*'s findings. To reflect changes in recommendations, especially with regards to the efficacy of maintenance BCG, EORTC published nomograms in 2016 for NMIBC patients receiving one to three years of BCG. They found grade and stage were the most important prognostic factors for progression. For recurrence, the most important prognostic factor was prior recurrence rate and number of tumours (7). However, there is difficulty in comparing this to Soria *et al.*'s data because the updated EORTC nomogram did not include patients with CIS.

Soria *et al.*'s study confirms the worsening survival outcomes in patients that progress to muscle invasive disease. Those that progressed prior to RC had worse outcomes compared to those where progression was detected on post cystectomy histology. A significant percentage of patients (22%) were upstaged at RC. Similarly, high rates of upstaging at RC have been widely

published with figures varying from 21–57% (8,9). May *et al.* found that in 210 patients with upstaging at RC, 5-year cancer specific survival reduced from 86% in the  $< pT2N0$  group to 60% in the  $> pT2N0$  and worse still in the node positive group at 34% (9). This is the crux of the argument for early cystectomy as it is widely accepted that delay increases the chance of disease progression and worsens survival outcomes.

There are few shortcomings in the data used in Soria *et al.*'s study which the authors have acknowledged. These can perhaps be explained by the long period of time over which data was acquired; 1991–2011. Unsurprisingly, urology practice and recommendations have developed and adapted over this 20-year period. One fundamental issue revolves around BCG treatment. Only 142 of the 509 (28%) patients included in the study received maintenance BCG. Bohle *et al.*'s meta-analysis recommends that at least 1 year of BCG be given in a maintenance schedule (10) and current EAU guidelines go a step further stating 3-year maintenance is the most effective (5). Thirty years ago, maintenance BCG was not the 'norm' and practices have changed significantly since then. This makes it difficult to draw firm conclusions on the oncological outcomes of BCG treatment in high risk tumours if only 28% of the patients received what is currently recommended as the optimal BCG schedule. This factor may make the study less generalizable to current practice. Similar criticism can be levelled at the rates of second resection. EAU guidelines recommend all T1 tumours have a second resection as well as those without muscle in the first resection (5). The largest meta-analysis including 3,566 patients found significant residual tumour, up to 50%, and significant upstaging, 10%, at second resection in T1 patients (11). Furthermore, it has been shown that residual T1 disease at re-resection is a bad prognostic sign for recurrence and progression and may influence the decision for early RC (12). The authors appreciate this limitation as they inform us in their conclusion that only 258 (51%) of the patients underwent re-resection. Similarly, we do not know the rates of muscle inclusion in the study data and if we combine this with the low re-resection rates there is serious concern regarding incomplete resection of tumour leading to significant under-staging in this study.

There is little to no mention of neoadjuvant chemotherapy (NAC) or cystectomy technique in Soria *et al.*'s study. In fairness, there is scant guidance on the role of NAC in patients with T1G3 disease undergoing RC and it is not recommended by the current guidance.

There is also limited guidance to suggest whether NAC is beneficial in those that progress to muscle invasive disease prior to RC. However, given cisplatin-based combination NAC has been shown to improve overall 5-year survival by 8% in those with muscle invasive disease (13), it is an important variable to consider. Indeed, it may have had a bearing on the survival outcomes described in the study. With regards to cystectomy technique, it can be assumed that the majority were performed by the open approach. From 2008 onwards, the role of minimally invasive robotic techniques has increased due to emerging technology and surgeon experience. Analysis of the US national cancer database reveals that 34.1% of all cystectomies in 2013 were performed by the minimally invasive approach (14). Studies to date have failed to attribute an oncological advantage to open or minimally invasive techniques, however, this may change with time and for example, facilitate the timely administration of adjuvant chemotherapy with improved outcomes.

Increased interest in the biochemical markers of BCG response, mirrors the growing understanding of the molecular and immunological basis of bladder cancer and BCG response. Fluorescence in situ hybridization (FISH) represents an old technology with a new application. It was originally developed for cancer detection but has since been studied as a marker for predicting BCG failure. A positive FISH result at 3 months correlates with 46% risk of tumour recurrence compared to an 8% risk with a FISH negative result ( $P < 0.001$ ) (15). Overexpression of p53, a cell cycle regulator, is well investigated and has been associated with disease progression (16). Multiple other molecular markers have been suggested including surviving, Ki-67, ezrin and bcl-2 to name a few. Many of these studies suffer from a lack of standardised measurement and diagnostic cut-offs (17). Further proposed biomarkers include revisiting urinary cytokines with new technologies, measurement of clinical response through surrogates such as skin reactivity in anti-tuberculin reaction and leukocyturia, as well as the genomic sequencing of BCG responders and non-responders. It remains to be seen whether these new technologies will translate into clinical practice.

In conclusion, Soria's paper re-ignites the longstanding debate regarding early cystectomy for T1G3 disease, and confirms our existing understanding of prognostic factors. Whilst they have provided an interesting perspective by investigating the risk factors for RC, the clinical benefit is not convincing, especially considering how explicit current EAU guidelines are in their recommendation for RC in the

'highest risk' subcategory. Furthermore, there are question marks over the clinical applicability of their data, many of the patients received treatment almost thirty years ago, at a time when maintenance BCG and re-resection were not recommended. Looking forward, future well designed randomised prospective trials comparing BCG and early RC will be invaluable, albeit difficult to facilitate. Perhaps the answer will be found in emerging technologies. As our understanding of the molecular and immunological basis of BCG response improves, biomarkers may be able to predict those destined to fail BCG treatment, surpassing our current clinicopathological predictors. Armed with this information, urologists will be able to offer sensible advice to their patients when faced with the dilemma of highly morbid cystectomy versus the potential ineffectiveness of BCG in high risk NMBIC.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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