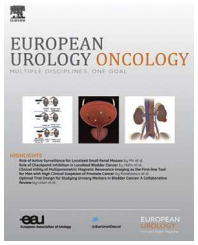

Article:
Shariat, S., Gontero, P. and Catto, J.W.F. orcid.org/0000-0003-2787-8828 (2019) How to treat a patient with T1 high-grade disease and no tumour on repeat transurethral resection of the bladder? European Urology Oncology. ISSN 2588-9311

https://doi.org/10.1016/j.euo.2019.07.006

EUROPEAN UROLOGY ONCOLOGY XXX (2019) XXX–XXX

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com



European Association of Urology

How to Treat a Patient with T1 High-grade Disease and No Tumour on Repeat Transurethral Resection of the Bladder?

Shahrokh Shariat [a,*], *Paolo Gontero* [b], *James W.F. Catto* [c]

[a] *Department of Urology, Medical University of Vienna, Vienna, Austria;* [b] *University of Studies of Torino, Torino, Italy;* [c] *Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK*

Article info

Article history:
Accepted July 10, 2019

Associate Editor:
Gianluca Giannarini

Keywords:
T1 grade 3 disease
Intravesical therapy
Radical cystectomy

Abstract

A relatively young (64-yr old) long-term heavy smoker but otherwise very healthy man is diagnosed with a primary unifocal left-side tumour (urothelial, T1 high grade), but no lymphovascular invasion and no variant histology. We discuss whether treatment with intravesical bacillus Calmette-Guérin vaccine will be sufficient or early radical cystectomy is at least equally preferred regarding patient benefit, safety, and quality of life.

Patient summary: A patient with a single high-grade T1 bladder tumour without aggressive features (eg, lymphovascular invasion or variant tumour aspects) will be adequately treated with bacillus Calmette-Guérin intravesical therapy delivered into the bladder, followed by 3 yr of maintenance. However, all decisions should be taken with the patient in a shared decision-making process, including a discussion regarding removal of the bladder.

* Corresponding author. Department of Urology, Medical University of Vienna, Vienna General Hospital, Währinger Gürtel 18-20, Vienna A-1090, Austria. Tel. + 43 1 404 0026 150, Fax: +43 1 404 0023 320.
E-mail address: shahrokh.shariat@meduniwien.ac.at (S. Shariat).

1. Case presentation

This case presents a 64-yr-old, healthy man who noted microscopic haematuria and immediately sought an appointment with the physician. He was a long-term heavy smoker, which alerts the physician to bladder cancer. The standard practice in Austria includes an ultrasound scan, which revealed a small lesion in the bladder of this patient. Cytology is suspicious for high-grade cancer, and transurethral resection of the bladder (TURB) reveals a single primary unifocal 2.0-cm tumour on the left side.

During TURB with blue light using hexaminolevulinate (Hexvix), there were two foci of concomitant carcinoma in situ (CIS). The pathology revealed PT1 high grade without lymphovascular invasion or variant histology, with two foci of CIS, that is, a pure urothelial T1 2.0-cm unifocal non–muscle-invasive bladder cancer (NMIBC) lesion.

At this point, the physician opted for a repeat TURB (re-TURB). This revealed no residual tumour, and the computed tomography (CT) urogram was normal as well. The question is: What is the best treatment for this patient?

2. Option A: the case for conservative therapy

Why should we choose conservative intravesical treatment in this patient—a healthy 64-yr-old man with T1 grade 3

https://doi.org/10.1016/j.euo.2019.07.006

Please cite this article in press as: Shariat S, et al. How to Treat a Patient with T1 High-grade Disease and No Tumour on Repeat Transurethral Resection of the Bladder?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.07.006

(T1G3) NMIBC, no residual tumour after re-TURB, and a negative CT urogram?

2.1. Evidence

2.1.1. BCG is effective in T1G3

Intravesical immunotherapy with bacillus Calmette-Guérin (BCG) is generally effective for T1G3 disease. A large retrospective study of 2530 T1G3 patients [1] treated with BCG and followed up for an average of 5.2 yr found that 79% of patients did not experience disease progression; only 23% received radical cystectomy, meaning that >70% kept their bladder beyond 10 yr and the cancer-specific death rate was as low as 9%.

2.1.2. There is no proof that cystectomy is superior to BCG in T1G3

No prospective study has compared BCG with cystectomy in T1G3 NMIBC. Retrospective comparative series have pointed out a potential advantage of radical cystectomy only in T1G3 associated with negative prognostic factors such as CIS [2]. However, radical cystectomy is far from guaranteeing cure in T1G3. In the milestone cystectomy series from Stein et al [3], patients who received a radical cystectomy for a true T1G3 (ie, T1 disease in the radical cystectomy specimen) had a 20% risk of recurrence at 10 yr. Since bladder cancer recurring after radical cystectomy is usually only amenable to palliative treatment, it is reasonable to assume that no more than 80% of T1G3 patients will survive despite early radical cystectomy, figures that almost overlap the 10-yr cancer-specific survival of 85% found in a large BCG series [1].

2.1.3. No residual tumour at re-TURB carries a good prognosis

According to the current guidelines [4], patients with any T1 disease should undergo a mandatory re-TURB. Does the absence of residual disease at re-TURB translate into a better disease outcome? In 710 NMIBC patients with T1G3 disease [5], the risk of progression to muscle-invasive bladder cancer differed widely, depending on the pathologic results of a re-TURB. Patients who were found to be T0 at re-TURB had the lowest risk of progression at 5 yr (9%).

Similar variability in outcomes of T1G3 according to re-TURB findings was observed in a more recent and larger study of T1G3 in patients who subsequently received BCG [6]. Out of a total of 951 patients undergoing a re-TURB, 267 patients without a residual tumour had the lowest risk of progression: 14% at 10 yr, with cancer-specific survival of 94% (cancer-specific death rate 6%).

A retrospective analysis assessed the outcomes of radical cystectomy for T0 in the surgical specimen [7]. Results were reported for a subgroup of 68 patients with T1 disease with no residual tumour in the radical cystectomy specimen, showing a 16% recurrence rate and a 5.2% death rate at 10 yr. This observation indicates that the prognosis for T1G3 patients receiving early radical cystectomy without evidence of disease in the surgical specimen overlaps that of conservatively treated T1G3 patients found to be T0 in the re-TURB results. Even for its best scenario, radical cystectomy does not seem to confer any advantage over conservative therapy.

Table 1 – Single or combinations of prognostic factors predicting a "very high" risk of progression in T1G3 disease.

Prognostic factor	Risk of progression
Persistent T1 disease at re-TURB	25–75%
T1G3 with CIS + tumour size >3 cm + age >70 years	60%
T1G3 + female gender + CIS prostatic urethra	40%
T1 with depth of invasion >3 mm and diameter of invasive focus >6 mm	100%
Variant histology (micropapillary)	24%
Lymphovascular invasion	34%

CIS = carcinoma in situ; Re-TUR = repeat transurethral resection.

2.1.4. T1G3 with no negative prognostic factors is a good indication for conservative therapy

A number of prognostic factors, alone or in combination with T1G3, are notoriously deemed to negatively affect the risk of progression [8].

As shown in Table 1, when T1G3 is associated with one or more negative prognostic factors, the risk of progression becomes significant to the point that early radical cystectomy is strongly advocated. Of note, the current clinical case of a T1G3 with a limited quantity of concomitant CIS that was found to have no residual tumour on re-TURB has none of the mentioned negative prognostic factors, thus representing the ideal candidate for conservative therapy.

2.2. Conclusion and treatment recommendation

Based on the current evidence, solitary T1G3 disease with no residual tumour at re-TURB should ideally be treated conservatively with intravesical BCG. This patient carries a relatively low risk of progression, especially because there are no other bad prognostic features. There is no proof that early radical cystectomy, even in the best scenario of a pathologic T0, would have a better prognosis. Radical cystectomy does not guarantee cure of a T1G3 tumour; rather it conveys a risk of cancer-specific death as high as 20%. Hence, patients such as the one discussed here can be spared aggressive treatment and given the chance to maintain their native bladder in up to 75% of cases at no additional risk of death.

3. Option B: the case for radical cystectomy

3.1. Evidence

3.1.1. Quality control of the case: possibility of pathologic variants

When considering patients such as the one discussed in this paper, the first step is to re-review the pathology and radiology. We have multidisciplinary treatment (MDT) meetings are conducted in the UK, where such reviews are performed. Patients with high-grade or muscle-invasive bladder cancer are cared for in cancer centres following MDT review and National Institute for Health and Care Excellence (NICE) guidance [9]. A review of imaging and

Please cite this article in press as: Shariat S, et al. How to Treat a Patient with T1 High-grade Disease and No Tumour on Repeat Transurethral Resection of the Bladder?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.07.006

pathology is performed by specialised uroradiologists and uropathologists, who may identify differences with the initial report and pathologic variants of urothelial cell carcinoma. In a recent series of 589 TURB cases [10], variant histology was missed in 44% of the referrals coming into the MDT review process. These variant cancers are usually more aggressive, and so it is important to identify this.

3.1.2. *Risk-benefit of BCG*

Assuming that the diagnosis of high-risk NMIBC without the presence of pathologic variants is correct, in cases such as the present one, Dr. Catto's centre offers three options: intravesical BCG, radical cystectomy, or a clinical trial (eg, BRAVO [11] or IROC [12]). Dr. Gontero has provided an excellent summary of the general advantages of intravesical BCG in the previous section of this article. However, Dr. Catto's personal opinion is that the support in favour of BCG appears more robust than the evidence suggests (although it can be admitted that many uro-oncologists may not share this concern).

For example, much of the evidence for the benefit of BCG comes from Sylvester et al's [13] first meta-analysis in 2002 (updated with new data in 2005 [14]). This showed a 27% relative reduction of disease progression with BCG (in the same population as the present patient case). This created the view that BCG is associated with a real reduction in progression (and recurrence) of disease. In other words, (1) the overall progression rates seen with BCG are low and many patients keep their bladders; (2) keeping the bladder is beneficial because it is presumed that one has better quality of life (QOL) than after radical cystectomy; (3) the Sylvester meta-analysis seemed to suggest that BCG is less toxic than radical cystectomy; and (4) if BCG fails, a salvage radical cystectomy is possible with no drawbacks. All these apparent benefits support the concept that delaying a radical cystectomy has no, or very little, harm.

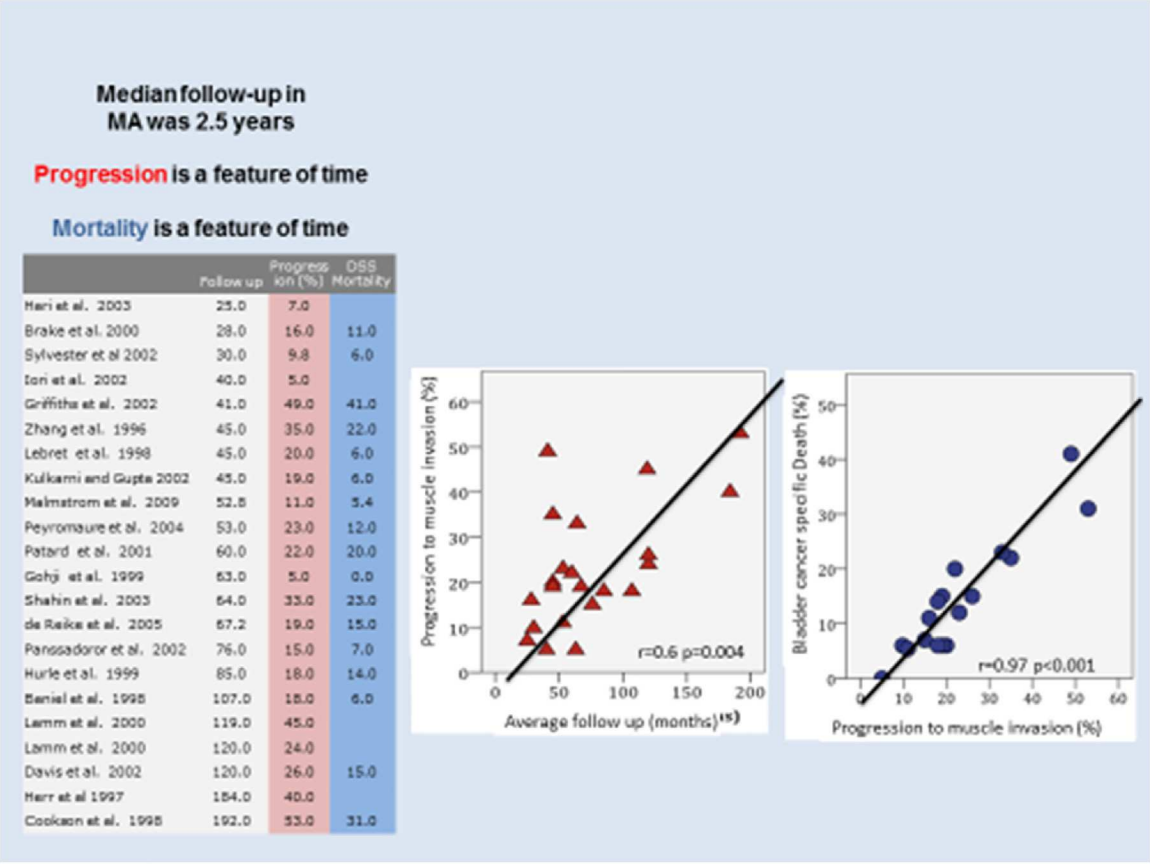
However, each of these assumptions may not be proved or necessarily true as outlined below.

3.1.3. *Critique of BCG meta-analyses: progression versus recurrence*

Disease progression and mortality from T1G3 high-risk NMIBC are clearly correlated with time after initiation of therapy (eg, the data from Kulkarni et al [15] as plotted in Fig. 1), illustrating that both variables are associated with time [8].

The first concern regarding the Sylvester meta-analyses is that the median follow-up was only 2.5 yr. Since many of the events would not have occurred in that population at that stage, this duration for the assessment of disease progression and mortality is premature for supporting the analysis' conclusion regarding the efficacy of BCG therapy.

There is also concern about the disease cohorts in the Sylvester meta-analysis. Whilst most clinicians use BCG for high-grade NMIBC (as for this patient), most patients in



	Follow up	Progression (%)	DSS Mortality
Heri et al. 2003	25.0	7.0	
Brake et al. 2000	28.0	16.0	11.0
Sylvester et al 2002	30.0	9.8	6.0
Ioni et al. 2002	40.0	5.0	
Griffiths et al. 2002	41.0	49.0	41.0
Zhang et al. 1996	45.0	35.0	22.0
Lebret et al. 1998	45.0	20.0	6.0
Kulkarni and Gupta 2002	45.0	19.0	6.0
Malmstrom et al. 2009	52.8	11.0	5.4
Peyromaure et al. 2004	53.0	23.0	12.0
Patard et al. 2001	60.0	22.0	20.0
Gohji et al. 1999	63.0	5.0	0.0
Shahin et al. 2003	64.0	33.0	23.0
de Reijke et al. 2005	67.2	19.0	15.0
Panssadoror et al. 2002	76.0	15.0	7.0
Hurle et al. 1999	85.0	18.0	14.0
Daniel et al. 1998	107.0	18.0	6.0
Lamm et al. 2000	119.0	45.0	
Lamm et al. 2000	120.0	24.0	
Davis et al. 2002	120.0	26.0	15.0
Herr et al 1997	154.0	40.0	
Cookson et al. 1998	192.0	53.0	31.0

Fig. 1 – Correlation of disease progression and mortality with duration of follow-up. MA = meta-analysis. Adapted from Kulkarni et al [15].

these meta-analyses were of intermediate risk. According to the European Organisation for Research and Treatment of Cancer tables [14], the risk of progression is 5% for grade 1, 10–15% for grade 2, and 25–75% for grade 3 NMIBC. In the meta-analyses Sylvester et al [13, Table 2], only 7.6% of the tumours treated with BCG were high-grade disease, and as a result, these percentages for high-grade data do not apply for the population in the present case.

A more recent meta-analysis of the data of 2820 patients [16] found no statistically significant benefit of BCG over other treatments regarding the risk of progression, and certainly not the 27% relative protection against progression reported for BCG in the Sylvester meta-analyses. Across the entire population of the individual patient meta-analysis by Malmstrom et al [16], there was very little difference in mortality.

Therefore, in total, we have to question whether BCG is as effective as we thought.

3.1.4. QOL with BCG

A further key unresolved question is the supposed benefit of intravesical BCG therapy versus that of radical cystectomy on QOL. In his personal experience as a busy urologist, a member of patient focus and social media groups, and an advisor to one of the UK charities, Dr. Catto hears that many patients worry about BCG (ie, how is their cancer responding) and finds that it has many side effects. Although the patients may not communicate these to their physicians, they have anxiety and concern about their urinary symptoms, the number 1 among them being anxiety about side effects of BCG in particular (including cystitis and bladder pain), as well as concern about whether there is a bladder tumour and whether they should worry about these things. All these things are extremely bothersome for patients, and if we look at the very few prospective data, they are not reporting fantastic QOL on BCG that is allowing them to preserve their bladder.

Even though published results in well-controlled trials show a good compliance rate with BCG [8,16,17], in practice, only about one-third of the patients complete 3 yr with BCG; approximately half of the patients do not complete the 3-yr stop because of perceived lack of efficacy [18,19], and the other half stop BCG due to toxicity [8,17,20]. Many patients complete only about 1 yr of BCG because of issues with tolerability and practicality of BCG [8,16–18].

3.1.5. QOL and recovery after radical cystectomy

Although based on little evidence, most physicians know that within 6 mo after cystectomy most patients find that their QOL is back to where it was before the discovery of their high-grade bladder cancer, if not better. From a small study (81 patients) interviewed preoperatively [21], most reported a return to preoperative QOL at 1 yr after cystectomy. Overall, nine out of 10 patients in the UK reported the same or better QOL at 6 mo after cystectomy versus only one in 10 who had complications; although this is <100%, it appears that after cystectomy a patient's QOL approaches the normal value reasonably quickly.

In addition, the modern cystectomy procedure is no longer the morbid option that it used to be. The mortality rate is low, and current enhanced recovery after surgery rates mean that patients are being discharged to go home much faster and they are much better [12].

3.1.6. Is delay of radical cystectomy detrimental?

One of the arguments in favour of intravesical therapy with BCG is the assumption that salvage radical cystectomy (for BCG failures) can be performed without any detrimental impact on cancer survival rates. Various series looking at this comparison have been published [2,22–25], with some showing no benefit of delaying radical cystectomy, some showing benefit of delaying surgery, and some finding harm to the patient with delay (recently reviewed by Klaassen et al [8]). It seems logical that if a physician delays definitive treatment for a period of time (eg, for a trial of BCG) and finds a progressing invasive tumour, then the patient outcome will be worse than that if the patient is treated with immediate definitive radical cystectomy. Given improvements in radical cystectomy [26], one would wonder whether the time for primary cystectomy is now.

3.2. Conclusion and treatment recommendation

There appears to be an equipoise between the two treatments, intravesical BCG and radical cystectomy, regarding patient benefit, safety, and QOL. For example, once the number of hospital visits required with BCG is added, the pros and cons of intravesical therapy versus radical cystectomy become a lot more equivalent. Further, remembering that most of these patients are mid-70-yr-old individuals, the QOL impact of losing the bladder and sexual function for an average patient is probably similar between the two treatment strategies. As such, patients should choose their option, but they should be fully aware of the risks and benefits of both approaches.

4. Discussion of treatment options

T1HG bladder cancer constitutes approximately 25% of incident bladder cancers. It has a heterogeneous natural history, with large variation in reported oncologic outcomes. Radical cystectomy is considered the best chance at cure, albeit with a high risk of morbidity, and is overtreatment for some patients. Treatment with BCG allows bladder preservation but may risk disease progression. A number of studies point to the danger in delaying radical cystectomy in patients with high-risk disease, and if possible, these patients have the most to gain from aggressive, early radical therapy. Optimal risk stratification is essential to individualise patient management, in order to offer radical cystectomy to those at the greatest risk of disease progression, while allowing others to safely pursue bladder-preserving approaches such as intravesical BCG.

Ideal prognostic factors would identify patients who may safely be managed with local therapy (ie, TURB plus intravesical BCG therapy), and differentiate patients who are at a high risk of progression and would therefore

Please cite this article in press as: Shariat S, et al. How to Treat a Patient with T1 High-grade Disease and No Tumour on Repeat Transurethral Resection of the Bladder?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.07.006

benefit most from aggressive treatment (ie, early radical cystectomy).

For the majority of clinicians, risk stratification of T1 tumours currently relies on standard clinicopathologic variables such as the presence of concomitant CIS, tumour multifocality, tumour size >3 cm, deep lamina propria invasion, and residual T1 after restaging TURB. The occurrence of more than one (ie, multiple) of these risk factors at T1HG diagnosis distinguishes candidates who should be advised to undergo immediate radical cystectomy. These specific high-risk features include any of the following: younger patients with long life expectancy, extensive concomitant CIS, multifocal T1HG tumours, and T1HG disease at re-TURB [27].

Likewise, identification of high-grade disease at the first cystoscopic follow-up (BCG refractory) and/or T1 or prostatic urethral disease at any point during follow-up identifies candidates for early radical cystectomy [4]. Pathologic substaging has been proposed as an approach to risk stratify T1 tumours more accurately. Specifically, T1 tumours have been subclassified as T1a, T1b, or T1c, based on invasion above, into, or beyond the muscularis mucosa-vascular plexus. More recently, a meta-analysis highlighted the prognostic value of pathologic substaging in 15 215 patients from 73 studies, of whom 97.9% had T1 high-grade disease [28]. T1b/c substage, which was evaluated in 11 studies of 1431 patients, was identified as the greatest risk factor for progression (hazard ratio [HR] 3.34) and cancer-specific mortality (HR 2.02). Unfortunately, however, the muscularis mucosa–vascular plexus may not be evident in up to one-third of cases precluding pathologic substaging. Accordingly, other pathologic substaging systems have been proposed based on the depth of invasion measured in millimetres. Indeed, we and others have supported a substaging system that dichotomised T1 into microinvasive (T1mic, depth ≤0.5 mm) and extensive (T1ext, depth >0.5 mm) tumours [29].

In addition to these factors, there are several factors that are very strong indicators of the need for an early radical cystectomy: lymphovascular invasion and select variant histologies. The presence of lymphovascular invasion represents a particularly important adverse prognostic feature in NMIBC, as this entity has been associated with significantly increased risks of progression, metastasis, and mortality [30,31].

Similarly, any patient with T1HG associated with select variant urothelial histologies (ie, micropapillary, nested, plasmacytoid, or sarcomatoid) are at a significantly increased risk of disease recurrence, progression, and mortality. These patients are at increased risks of advanced disease and lymph node metastasis at the time of radical cystectomy. Micropapillary bladder cancer is one of the more common variant histologies with a particular aggressive phenotype for which BCG is probably less effective. While some authors advocate proactive immediate radical cystectomy in patients with T1 disease with micropapillary variant component, others argue that bladder-conserving strategy such as BCG therapy can be beneficial, with immediate radical cystectomy not being superior to conservative measures [32].

It is evident that the current risk stratification of T1 based on standard clinicopathologic features remains imperfect. Younger patients with longer life expectancy; extensive CIS; variant histology such as nested, micropapillary, plasmacytoid, or sarcomatoid; prostatic urethral involvement; lymphovascular invasion; or residual T1HG disease at re-TURB [33] should be considered for immediate radical cystectomy, whilst patients without these features could reasonably be offered BCG, with early radical cystectomy reserved for those with recurrent high-grade disease despite adequate BCG therapy. Obviously, all decisions must be made with the patient together in a shared decision-making process based on scientific evidence and personal preferences of the patient and his family. Conditions for a bladder-preserving strategy include nononcologic factors such as no/minimal irritative voiding symptoms, compliance with a strict long-term follow-up, and readiness to change strategy with early treatment failure prompting treatment with radical cystectomy.

5. Summary and final treatment recommendation

The current case, a rather young man with a unifocal 2-cm T1HG tumour, without lymphovascular invasion or variant histology, but with two small areas of concomitant CIS and T0 on re-TURB, is certainly a patient with whom the risks, benefits, and alternatives to immediate radical cystectomy would be discussed, but for whom a trial of induction intravesical BCG with the plan for a 3-yr maintenance therapy would be suggested.

Current strategies for diagnosis, risk stratification, and treatment are imperfect, but emerging knowledge and molecular approaches can help us guide our patients with an optimised individualised evidence-based treatment strategy. In light of the limitations of standard clinicopathologic features as prognostic variables for patients with T1 disease, it is clear that a need exists for more refined risk stratification. In this regard, there has been a growing effort to develop a molecular classification of bladder cancer [34,35].

New immune strategies and new drug (chemotherapy and immunotherapy) combinations, in addition to new biomarkers, will hopefully help urologists further personalise therapies for patients with T1 high-grade disease and ultimately improve outcomes in these difficult to manage, high-risk patients.

Author contributions: Shahrokh Shariat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shariat, Catto, Gontero.
Acquisition of data: Shariat, Catto, Gontero.
Analysis and interpretation of data: Shariat, Catto, Gontero.
Drafting of the manuscript: Shariat, Catto, Gontero.
Critical revision of the manuscript for important intellectual content: Shariat, Catto, Gontero.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: Shariat.

Supervision: Shariat.
Other: None.

Financial disclosures: Shahrokh Shariat certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Shahrokh Shariat reports no relevant personal financial relationships. Paolo Gontero acknowledges the following support: consultancies: Astellas and Algena; honoraria: Janssen and Cepheid. James W.F. Catto acknowledges the following support: grants or funding: Astellas and GSK; advisory boards: Astra Zeneca, BMS, and GSK; honoraria: Roche, MSD, and Nucleix.

***Funding/Support and role of the sponsor*:** None.

Acknowledgments

Origin of Academic Content: This article has been developed from an interactive, multi-faculty scientific session presented during the 33rd Annual EAU Congress in Copenhagen, March 2018, with acknowledgment to the Co-chairs of the session: H. Barton Grossman, MD; Ashish Kamat, MD; and Arnulf Stenzl, MD, PhD. Acknowledgment is also given to Dr. Grossman and Dr. Kamat for their development of the multi-faculty, interactive format of this article, and for their editorial review of the draft manuscript for submission to *European Urology Oncology*.

Open Access: Cepheid® provided funding to allow Open Access for this article.

References

[1] Gontero P, Sylvester R, Pisano F, et al. Prognostic factors and risk groups in T1G3 non-muscle-invasive bladder cancer patients initially treated with Bacillus Calmette-Guérin: results of a retrospective multicenter study of 2451 patients. Eur Urol 2015;67:74–82.
[2] Denzinger S, Fritsche HM, Otto W, Blana A, Wieland WF, Burger M. Early versus deferred cystectomy for initial high-risk pT1G3 urothelial carcinoma of the bladder: do risk factors define feasibility of bladder-sparing approach? Eur Urol 2008;53:146–52.
[3] Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001;19:666–75.
[4] Babjuk M, Böhle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol 2017;71:447–61.
[5] Herr H, Donat SM. A re-staging transurethral resection predicts early progression of superficial bladder cancer. BJU Int 2006;97:1194–8.
[6] Palou J, Pisano F, Sylvester R, et al. Recurrence, progression and cancer-specific mortality according to stage at re-TUR in T1G3 bladder cancer patients treated with BCG: not as bad as previously thought. World J Urol 2018;36:1621–7.
[7] Tilki D, Svatek RS, Novara G, et al. Stage pT0 at radical cystectomy confers improved survival: An international study of 4,430 patients. J Urol 2010;184:888–94.
[8] Klaassen Z, Kamat AM, Kassouf W, et al. Treatment strategy for newly diagnosed T1 high-grade bladder urothelial carcinoma: new insights and updated recommendations. Eur Urol 2018;74:597–608.
[9] National Institute for Health and Care Excellence (NICE). Managing non-muscle-invasive bladder cancer. http://pathways.nice.org.uk/pathways/bladder-cancer. (NICE Pathway last updated: 23 July 2019).
[10] Shah RB, Montgomery JS, Montie JE, Kunju LP. Variant (divergent) histologic differentiation in urothelial carcinoma is under-recognized in community practice: impact of mandatory central pathology review at a large referral hospital. Urol Oncol 2013;31:1650–5.
[11] Oughton JB, Poad H, Twiddy M, et al. Radical cystectomy (bladder removal) against intravesical BCG immunotherapy for high-risk non-muscle invasive bladder cancer (BRAVO): a protocol for a randomised controlled feasibility study. BMJ Open 2017;7:e017913.
[12] Catto JWF, Khetrapal P, Ambler G, et al. Multidomain quantitative recovery following radical cystectomy for patients within the robot-assisted radical cystectomy with intracorporeal urinary diversion versus open radical cystectomy randomised controlled trial: the first 30 patients. Eur Urol 2018;74:531–4.
[13] Sylvester RJ, van der Meijden AP, Witjes JA, Kurth K. Bacillus Calmette-Guérin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. J Urol 2005;174:86–91.
[14] Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Euro Urol 2006;49:466–77.
[15] Kulkarni GS, Hakenberg OW, Gschwend JE, et al. An updated critical analysis of the treatment strategy for newly diagnosed high-grade T1 (previously T1G3) bladder cancer. Eur Urol 2010;57:60–70.
[16] Malmstrom P-U, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomized studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol 2009;56:247–56.
[17] Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000;163:1124–9.
[18] Cookson MS, Herr HW, Zhang ZF, Soloway S, Sogani PC, Fair WR. The treated natural history of high risk superficial bladder cancer: 15-year outcome. J Urol 1997;158:62–7.
[19] Thomas F, Noon AP, Rubin N, Goepel JR, Catto JW. Comparative outcomes of primary, recurrent and progressive high-risk non-muscle invasive bladder cancer. Eur Urol 2013;63:145–54.
[20] Lamm DL, van der Meijden PM, Morales A, et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol 1992;147:596–600.
[21] Hardt J, Filipas D, Hohenfellner R, Egle UT. Quality of life with bladder carcinoma: first results of a prospective study. Qual Life Res 2000;9:1–12.
[22] Thalmann GN, Markwalder R, Shahin O, Burkhard FC, Hochreiter WW, Studer UE. Primary T1G3 bladder cancer: organ preserving approach or immediate cystectomy? J Urol 2004;172:70–5.
[23] Herr HW, Donat SM. Outcome of patients with grossly node positive bladder cancer after pelvic lymph node dissection and radical cystectomy. J Urol 2001;165:62–4.
[24] Schrier BP, Hollander MP, van Rhijn BW, Kiemeney LA, Witjes JA. Prognosis of muscle-invasive bladder cancer: difference between primary and progressive tumours and implications for therapy. Eur Urol 2004;45:292–6.
[25] Lambert EH, Pierorazio PM, Olsson CA, Benson MC, McKiernan JM, Poon S. The increasing use of intravesical therapies for stage T1 bladder cancer coincides with decreasing survival after cystectomy. BJU Int 2007;100:33–6.
[26] Pang KH, Groves R, Venugopal S, Noon AP, Catto JWF. Prospective implementation of enhanced recovery after surgery protocols to radical cystectomy. Eur Urol 2018;73:363–71.
[27] Cumberbatch MGK, Foerster B, Catto JWF, et al. Repeat transurethral resection in non-muscle-invasive bladder cancer: a systematic review. Eur Urol 2018;73:925–33.

Please cite this article in press as: Shariat S, et al. How to Treat a Patient with T1 High-grade Disease and No Tumour on Repeat Transurethral Resection of the Bladder?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.07.006

[28] Martin-Doyle W, Leow JJ, Orsola A, Chang SL, Bellmunt J. Improving selection criteria for early cystectomy in high-grade T1 bladder cancer: a meta-analysis of 15,215 patients. J Clin Oncol 2015;33:643–50.
[29] Shariat SF, Weizer AZ, Green A, et al. Prognostic value of P53 nuclear accumulation and histopathologic features in T1 transitional cell carcinoma of the urinary bladder. Urology 2000;56:735–40.
[30] Mari A, Kimura S, Foerster B, et al. A systematic review and meta-analysis of the impact of lymphovascular invasion in bladder cancer transurethral resection specimens. BJU Int 2019;123:11–21.
[31] Mathieu R, Lucca I, Rouprêt M, Briganti A, Shariat SF. The prognostic role of lymphovascular invasion in urothelial carcinoma of the bladder. Nat Rev Urol 2016;13:471–9.
[32] Abufaraj M, Foerster B, Schernhammer E, et al. Micropapillary urothelial carcinoma of the bladder: a systematic review and meta-analysis of disease characteristics and treatment outcomes. Eur Urol 2019;75:649–58.
[33] Ferro M, Vartolomei MD, Cantiello F, et al. High-grade T1 on re-transurethral resection after initial high-grade T1 confers worse oncological outcomes: results of a multi-institutional study. Urol Int 2018;101:7–15.
[34] Passoni NM, Shariat SF, Bagrodia A. Concordance in biomarker status between bladder tumours at time of transurethral resection and subsequent radical cystectomy: results of a 5-year prospective study. Bladder Cancer 2016;2:91–9.
[35] Shariat SF, Passoni N, Bagrodia A, et al. Prospective evaluation of a preoperative biomarker panel for prediction of upstaging at radical cystectomy. BJU Int 2014;113:70–6.

Please cite this article in press as: Shariat S, et al. How to Treat a Patient with T1 High-grade Disease and No Tumour on Repeat Transurethral Resection of the Bladder?. Eur Urol Oncol (2019), https://doi.org/10.1016/j.euo.2019.07.006