Review Article

The rational and benefits of the second look transurethral resection of the bladder for T1 high grade bladder cancer

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Abstract: The second look transurethral resection of the bladder (TURB) represents a fundamental step in the treatment of papillary non-muscle invasive bladder cancer (NMIBC); it is therefore recommended by all guidelines. However, not all the literature agrees on its staging value and its ability to improve oncological outcomes of patients. Therefore, the purpose of this review is to evaluate the strengths and weaknesses of second look TURB, trying to depict its evolving role in the management of high grade NMIBC. Using Medline, a non-systematic review was performed including articles between January 2000 and June 2018. English language original articles, reviews and editorials were selected based on their clinical relevance. To date, TURB seems to be largely inadequate in retrieving a correct diagnosis and in removing all tumor tissue. Second look TURB maximizes staging accuracy, allows to clear residual cancer and yields prognostic advantages allowing key information to identify possible candidates for immediate radical cystectomy for very high risk T1HG tumors. Moreover, it seems to have a therapeutic benefit by improving recurrence- and progression-free survivals. However, few recent large studies showed that these advantages seem to be limited to patients without detrusor muscle present at first resection. Similarly, the presence of residual disease and the risk of upstaging are related to the presence of detrusor muscle in specimen. It could well be that in the future the presence of detrusor muscle would be a quality criteria to avoid an unnecessary second look TURB as shown by recent studies using the *en-bloc* resection technique. Finally, it has to be underlined that this is a surgical procedure not free of risks and complications and with a non-negligible impact on patients' quality of life, waiting lists and healthcare costs. Therefore, future studies trying to identify the criteria that may better allow which patients to select for a second look TURB while avoiding an unnecessary intervention with possible risks and associated cost are needed to allow a personalized approach to even this one size fits all strategy.

Keywords: Re-TUR; second look transurethral resection of the bladder (second look TURB); T1HG non-muscle invasive bladder cancer

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Introduction

Transurethral resection of the bladder (TURB), eventually followed by adjuvant intravesical chemotherapy or immunotherapy with bacillus Calmette-Guérin (BCG), is the standard diagnostic, staging and therapeutic approach for non-muscle invasive bladder cancer (NMIBC) (1). The initial TURB represents the most important step in the management of NMIBC, driving the diagnostic accuracy, the decision-making for selecting therapy and, consequently, the prognosis of the disease (2). Several issues suggest that the initial TURB alone could be an inadequate surgery in a non-negligible percentage of cases, resulting in a detrimental effect on oncological outcomes if not repeated, especially in patients harboring tumor invasion into the lamina propria (T1) (3). In this category of patients, international guidelines recommend a second look TURB to be performed 2–6 weeks after the first resection to confirm the stage and to get rid of residual disease if any exists (1). The second look TURB is, therefore, an important part of the optimal management of T1 NMIBC, by potentially adding essential information for risk-stratification and therapy. However, several recent publications questioned the ubiquitous necessity for a second look TURB, suggesting that it could be avoided in a well-selected group of patients with T1 NMIBC (4,5). The purpose of this review is to report the evidences on second look TURB, focusing on its strengths and weaknesses and trying to define its evolving future role.

Evidence acquisition

A non-systematic Medline/PubMed literature search was performed with different combinations of terms as "bladder cancer", "second look transurethral resection of the bladder", "second look TURB", "re-TURB", "upstaging", "T1HG bladder cancer", "outcomes" and "residual tumor". Time period included articles between January 2000 and June 2018, with special regards to those published in the last 5 years. Original articles, reviews and editorials were selected based on their clinical relevance.

Evidence synthesis

Current limitations of transurethral resection of the bladder

The goal of TURB is to make the correct diagnosis and to remove all visible lesions thereby avoiding or delaying disease recurrence and progression as well as preventing panurothelial disease (1). An accurate pathologic diagnosis is essential for precise risk assessment and therapy selection as well as tailored follow up scheduling (6). The quality of TURB appears to be one of the most important factors affecting the course of the disease, as shown by the variability in disease recurrence rates across centers and surgeons (7).

To date, TURB is, unfortunately, often inadequate in ensuring a correct diagnosis and complete removal of all tumor tissue; actually, between 30% to 60% of T1G3 tumors at TURB will end up being muscle-invasive at the radical cystectomy (8) and residual disease is found in up to 50% of patients when a second-look TURB is carried out within 6 weeks (9,10). One of the major limitations of TURB is its ability to ensure complete removal of all tumor afflicted tissues. The presence of detrusor muscle (DM) in the pathologic specimen has been considered as one of the quality indicators for an adequate TURB: the presence of DM is able to predict staging accuracy, residual tumor at second-look TURB and early recurrence. According to historical cohorts of patients with pT1 tumors, residual tumor at second look TURB is found in 83% of cases when no DM is submitted at the first resection compared to 74% when DM is present (11). Moreover, the presence of negative DM is an important quality control measure indicating a higher probability of correct staging and completeness of resection. For example, in patients with cT1, 49% of patients were upstaged to T2 if no DM was present compared to 14% when DM was present (3). Conversely, there is a very low probability of tumor upstaging at radical cystectomy when DM is present in the second-look TURB specimen before radical surgery (12). Recently, Mariappan *et al.* showed that the absence of DM in the first, apparently completed TURB specimen, is an independent predictor of early recurrence (13,14). However, despite several improvements in endoscopic technology, from tumor visualization to resection techniques, and even when TURB is performed by experienced surgeons at high-volume centers, DM can only be found in 50% to 80% of the specimens, depending on the series (11,14,15).

The second major drawback of TURB regards the diagnosis of concomitant carcinoma in situ (CIS), a well-known independent prognostic factor of negative outcomes (16,17). When TURB is performed under white light, the chance to miss a CIS, usually present as concomitant lesion in 10% to 40% of primary NMIBCs, reaches 40% (18). Similarly, the identification of other predictive factors

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such as the presence of lympho-vascular invasion (LVI) or histological variants is underestimated at the time of TURB when compared to the subsequent radical cystectomy, with a possible detrimental impact on treatment allocation (19-22). The inadequacy of TURB in identifying these features is probably a consequence of multiple factors, mainly regarding the quality of specimens submitted to pathology and the pathologic assessment itself. The diathermy during the resection results in cautery and crush artifacts (occurring more commonly during monopolar compared to bipolar resection), that are responsible for modifications in the microscopic appearance of the tissue, leading to possible misinterpretations and/or loss of information (23). Finally, the lack of specific expertise in uropathology can lead to inexact reporting (24): reported variance in NMIBC diagnosis among pathologists is not negligible with a discrepancy rate between of 18–20% referring pathologists and experienced uro-pathologists.

To overcome these limitations and to achieve a better diagnosis and staging, a second look TURB within 2–6 weeks from the first resection has been recommended for all incomplete resections and in case of high grade NMIBCs invading the lamina propria (T1) (1).

Strengths of second look TURB: an indispensable tool for the management of NMIBC

In a landmark study on second look TURB, 76% of 150 patients had residual cancer with almost one third being upstaged to MIBC (3). In a recent European cross-sectional survey, 54% to 98% of respondent urologists reported to regularly perform a second look TURB in patients with high-risk NMIBC, depending on the country of origin (25). Several contemporary studies have proven the advantages of second look TURB for high-risk NMIBC (*Table S1*) (26-29).

First, second look TURB maximizes diagnostic accuracy and allows to clear residual cancer. A recent retrospective series including 934 second look TURBs confirmed that 71.3% had residual cancer, even when excluding those being upstaged to T2 disease (4). The rate of residual disease remained as high as 77.6% despite the first resection being performed by an experienced surgeon (30). While other investigators have reported a lower rate of persistent disease, even in the best hands, residual disease remains in one of three patients, even when all first resections are deemed macroscopically complete (31-35). Even for pTa high-grade and low-grade cancers the rates of residual disease are as high as 41.4% (36) and 33.3%, respectively (37). When including patients with multiple negative prognostic factors, Kim *et al.* found that almost all patients had residual cancer at second look TURB (26). While the rate of upstaging varies between studies, in recent series, the rate remains approximately of one of 5–10 patients with initial T1 being actually muscle-invasive as revealed after the second look TURB (30,38,39). Even when an experienced surgeon feels that he has achieved a macroscopically complete first resection, upstaging to muscle-invasive disease remains too common to forego it (34,40). In a select group of 1,136 patients with clinical T1G3 at initial TURB who underwent radical surgery, 51.4% had indeed muscle-invasion and 33.4% had even non organ-confined disease (8). A recent meta-analysis of 29 studies found a pooled prevalence of 56% (95% CI, 48–63%) for residual tumor and 10% (95% CI, 6–14%) for upstaging to T2 in 3,566 and 2,556 patients, respectively (41).

Second, second look TURB pathology not only allows to identify patients who have a MIBC but also helps identify those who have NMIBC but are likely to fail BCG therapy and should, therefore, be considered for early radical cystectomy. Second look TURB pathology has, indeed, a strong prognostic value and is considered by some clinicians as the most significant predictor of early recurrence and progression (28,37,42). In a dataset of 710 NMIBC patients, Herr *et al.* have reported that a T1 at second look TURB yields a progression rate of 76% within 5 years (2). While this high progression rate has been questioned, the negative prognostic value of a T1 on second-look TURB is widely accepted. For example, Palou and colleagues confirmed the prognostic role of second look TURB pathology analyzing a cohort of 2,451 patients. T1 tumors at second look TURB were more likely to recur, progress and die from the disease; second look TURB pathology was the most important prognostic factor of these outcomes in a multivariate model including tumor multiplicity, concomitant CIS and BCG maintenance (5). However, in contrast to Herr *et al.*, only 25% of patients with T1 at second look TURB experienced disease progression at 5 years.

Third, second look TURB has a therapeutic benefit. According to several authors it decreases recurrence (30,31,33,40) and progression (26,32-34,40,43) while increasing cancer-specific (CSS) (4,34,38) and overall survival (OS) (4,38,44). When comparing second look TURB to observation, recurrences at 3 to 6 months cystoscopy are significantly lower, both for T1 and Ta high-grade tumors (30,40). Similarly, large second look TURB cohorts (32,33,40) and RCTs (26,34) yielded lower

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progression rates for patients who underwent a second look TURB compared to the control arms. A large retrospective study of prospectively collected data including 1,159 BCG-treated cases confirmed the positive impact on recurrence up to 5 years of a second look TURB (77.2% *vs.* 61.6% for second look TURB; P<0.001). A two-fold increased risk of 5-year progression and shorter median time to progression were also reported (33). Even if the translation of the survival impact of this decreasing recurrence and progression rates needs further confirmation, some authors question concrete benefits (40). However, there is a large body of evidence in favor of second look TURB (3,9,15,18). For example, a recently published report from the UK showed that patients who underwent a second look TURB had a statistically significant higher CSS (P=0.009) and OS (P<0.001) compared with those who did not. The authors hypothesized that re-resection may improve CSS and OS by appropriately identifying aggressive bladder cancers, leading to effective timely treatment (38). To date, the sole RCT reporting 5-years outcomes found cancer-specific deaths almost halved in the second look TURB group compared to the observation group (16.7% *vs.* 31.4%; P=0.038) with significantly longer time to recurrence- and progression-free survival (34).

Fourth, although rarely assessed, the downsides of second look TURB are rare. They include a potentially increased initial cost and potential complications such as prolonged bleeding (often managed conservatively) and infectious sequelae; high grade complications and life threatening events are the exception (26,34,40).

Overall, although confirmation of a clear survival improvement warrants further investigation, the benefits of second look TURB clearly out-weigh the risks and possible discomforts related to the procedure per-se as well as current alternatives. Thus, as highlighted by two just published systematic reviews, potential benefits of a timely second look TURB for T1HG on initial TURB favor a widespread adoption, until proven otherwise (45,46).

Weaknesses of second look TURB: is it possible to avoid it in well selected patients?

The necessity for all patients with high-risk papillary NMIBC to undergo a second look TURB within 2–6 weeks of the initial resection has been recently questioned. In a small retrospective series of 200 patients, second look TURB was found to be positively associated with short- but not with long-term oncological outcomes (40). Recently, Gontero *et al.*, in a multicentric retrospective study of 2,451 patients with T1G3/HG NMIBCs treated with BCG, reported that a second-look TURB had a positive impact on recurrence-free, progression-free, CSS and OS only in case of absence of DM in resection's specimen (4). Conversely, when DM was present, second look TURB did not improve the outcome for any of the endpoints; limitations of the study included its retrospective design and the low rate of second look TURB performed (38% of all patients). Similarly, Dutta *et al.* pointed out that staging inaccuracy in cT1 tumors at TURB is critically dependent from the presence of DM in the specimen, being upstaged at radical cystectomy 62% and 30% of patients without and with DM at TURB, respectively (9). Even more surprising were the findings reports by Gaya and colleagues from their single center series: the absence of DM was the only risk factor for tumor understaging, suggesting that, after a complete resection, when DM is present and tumor-free, a systematic second look TURB may not be necessary (47).

As previously shown, the presence of residual disease represents one of the most important factors in favor of second look TURB, due to its role in predicting progression to muscle-invasive disease. Palou *et al.* showed that residual disease at second look TURB is dependent from the presence of DM in the first resection; 65% and 86% in presence and absence of DM, respectively (5). The same association was found evaluating the rate of persistent T1 disease. One of the other factors associated with residual disease at second look TURB is tumor's size. Yucel *et al.* found that, in T1 disease, the risk of having a residual tumor was directly correlated with the diameter of the initial lesion (48). Successive reports confirmed these findings (49).

The presence of DM in TURB specimen seems, therefore, to play a potential role for selection of patients for second look TURB, even if not enough to drive decisions alone. Despite improvements in tumor resection and visualization, rates of DM in TURB specimens are still unsatisfactory, remaining around 70% even in current series and even when the resection is performed by a "senior surgeon" (50).

The advent of en-bloc resection technique (EBRT) for bladder cancer resection seems to be able to dramatically increase the rate of DM in pathologic specimen, independently for the source of energy used (monopolar *vs.* bipolar *vs.* laser). Kramer *et al.*, in a retrospective multicentric study of 221 patients treated with EBRT, reported the presence of DM in 97.3% of specimens (51); moreover, surgical margins at the horizontal edges of the

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lesion were free of tumor in all patients. Similar findings were reported in several retrospective series (52) and in a prospective single center study, in which all the patients receiving EBRT [90] harbored DM in their specimen (53). Previously, a prospective randomized study comparing conventional resection *vs.* EBRT showed a DM rate of 60% *vs.* 95%, respectively (54). A recently published review of EBRT literature showed the presence of DM in 96% of specimens (731 of 763 patients) (55). After EBRT, residual tumor rate at second look TURB is close to 0% (55). Migliari *et al.*, analyzing data from 58 patients treated with thulium laser EBRT, found no disease persistence at re-resection and cold biopsy of the tumor base (56).

In recent years, the advent on the market of new endoscopic technologies such as photodynamic diagnosis (PDD) and narrow band imaging (NBI) led to an improvement in tumor diagnosis and visualization, with consequent improved oncologic outcomes (18). One of the advantages of such techniques is probably due to an improved quality of TURB. Actually, the rate of DM in pathologic specimen is higher when the resection is performed under blue light compared to white light (77.6% *vs.* 61.9%) and the rate of residual disease at second look TURB lower (25.8% *vs.* 40.5%) (57). A systematic review of the literature reported a better residual tumor rate after PDD resection compared to white light TURB (4.5–32.7% *vs.* 25.2–53.1%, respectively); the odds ratio of residual tumor for PDD compared to white light was 0.28 while the relative risk of residual disease was 2.77-fold higher with white light (18).

Finally, it should be underlined that second look TURB implies a new surgical procedure requiring a general or locoregional anesthesia and, as all surgical procedures, is not free of risks and adverse events specifically in the elderly bladder cancer population (58). Moreover, it represents a cause of anxiety and discomfort for the patient that, in this period (2 to 6 weeks after TURB) is maybe still suffering from symptoms related to the first resection. Finally, the economic burden of a second look TURB and its impact on waiting lists should be taken into consideration.

Based on these evidences, it is conceivable and desirable that, in the next future, second look TURB could be avoided in a well-selected cohort of patients such as, for example, those with small lesions and those receiving EBRT under PDD when a macroscopically complete resection and DM in the specimen on pathologic assessment is achieved. Future studies are encouraged to test this hypothesis in order to improve bladder cancer management, patients' quality of life and health systems costs.

Conclusions

(I) Potential benefits of a timely second look TURB in patients with T1HG bladder cancer outweigh the risks compared to the alternatives.
(II) Advantages of second look TURB mainly rely on the limitations of first resection (staging inaccuracy and high rate of residual cancer).
(III) Detrusor muscle in the TURB specimen seems to abrogate some of the benefits of the second look TURB.
(IV) Due to the detrimental impact of second look TURB on patients' quality of life and health care costs, future studies aiming to identify a category of well-selected patients in which this procedure could be safely avoided are mandatory.
(V) Novel surgical endoscopic technologies such as EBRT and fluorescence cystoscopy seem to help to pave the way to achieving an optimal first TURB so that a second look TURB becomes unnecessary.

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Footnote

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

References

1. 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.
2. Herr HW, Donat SM. A re-staging transurethral resection predicts early progression of superficial bladder cancer. BJU Int 2006;97:1194-8.
3. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol 1999;162:74-6.
4. Gontero P, Sylvester R, Pisano F, et al. The impact of re-TUR on clinical outcomes in a large multi-centre cohort of T1-HG/G3 patients treated with BCG. BJU Int 2016;118:44-52.
5. Palou J, Pisano F, Sylvester R, et al. Recurrence, progression and cancer-specific mortality according to

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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.
6. Capogrosso P, Capitanio U, Ventimiglia E, et al. Detrusor Muscle in TUR-Derived Bladder Tumor Specimens: Can We Actually Improve the Surgical Quality? J Endourol 2016;30:400-5.
7. Brausi M, Collette L, Kurth K, et al. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. Eur Urol 2002;41:523-31.
8. Fritsche HM, Burger M, Svatek RS, et al. Characteristics and Outcomes of Patients with Clinical T1 Grade 3 Urothelial Carcinoma Treated with Radical Cystectomy: Results from an International Cohort. Eur Urol 2010;57:300-9.
9. Dutta SC, Smith JA, Shappell SB, et al. Clinical under staging of high risk nonmuscle invasive urothelial carcinoma treated with radical cystectomy. J Urol 2001;166:490-3.
10. Herr HW. Role of re-resection in non-muscle-invasive bladder cancer. ScientificWorldJournal 2011;11:283-8.
11. Herr HW, Donat SM. Quality control in transurethral resection of bladder tumours. BJU Int 2008;102:1242-6.
12. Dalbagni G, Herr HW, Reuter VE. Impact of a second transurethral resection on the staging of T1 bladder cancer. Urology 2002;60:822-4; discussion 824-5.
13. Mariappan P, Zachou A, Grigor KM, Edinburgh Uro-Oncology Group. Detrusor Muscle in the First, Apparently Complete Transurethral Resection of Bladder Tumour Specimen Is a Surrogate Marker of Resection Quality, Predicts Risk of Early Recurrence, and Is Dependent on Operator Experience. Eur Urol 2010;57:843-9.
14. Mariappan P, Finney SM, Head E, et al. Good quality white-light transurethral resection of bladder tumours (GQ-WLTURBT) with experienced surgeons performing complete resections and obtaining detrusor muscle reduces early recurrence in new non-muscle-invasive bladder cancer: validation across t. BJU Int 2012;109:1666-73.
15. Maruniak NA, Takezawa K, Murphy WM. Accurate pathological staging of urothelial neoplasms requires better cystoscopic sampling. J Urol 2002;167:2404-7.
16. 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-gu??rin: Results of a retrospective multicenter study of 2451 patients. Eur Urol 2015;67:74-82.
17. 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.
18. Rink M, Babjuk M, Catto JW, et al. Hexyl Aminolevulinate-Guided Fluorescence Cystoscopy in the Diagnosis and Follow-up of Patients with Non-Muscle-invasive Bladder Cancer: A Critical Review of the Current Literature. Eur Urol 2013;64:624-38.
19. Abufaraj M, Shariat SF, Foerster B, et al. Accuracy and prognostic value of variant histology and lymphovascular invasion at transurethral resection of bladder. World J Urol 2018;36:231-40.
20. Moschini M, Shariat SF, Freschi M, et al. Is transurethral resection alone enough for the diagnosis of histological variants? A single-center study. Urol Oncol Semin Orig Investig 2017;35.
21. Mathieu R, Lucca I, Rouprêt M, et al. The prognostic role of lymphovascular invasion in urothelial carcinoma of the bladder. Nat Rev Urol 2016;13:471-9.
22. Moschini M, D'Andrea D, Korn S, et al. Characteristics and clinical significance of histological variants of bladder cancer. Nat Rev Urol 2017;14:651-68.
23. Brausi M, Witjes JA, Lamm D, et al. A review of current guidelines and best practice recommendations for the management of nonmuscle invasive bladder cancer by the International Bladder Cancer Group. J Urol 2011;186:2158-67.
24. Hansel DE, Miller JS, Cookson MS, et al. Challenges in the pathology of non-muscle-invasive bladder cancer: a dialogue between the urologic surgeon and the pathologist. Urology 2013;81:1123-30.
25. Hendricksen K, Aziz A, Bes P, et al. Discrepancy Between European Association of Urology Guidelines and Daily Practice in the Management of Non-muscle-invasive Bladder Cancer: Results of a European Survey. Eur Urol Focus 2017. [Epub ahead of print].
26. Kim W, Song C, Park S, et al. Value of Immediate Second Resection of the Tumor Bed to Improve the Effectiveness of Transurethral Resection of Bladder Tumor. J Endourol 2012;26:1059-64.
27. 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.
28. Herr HW, Donat SM, Dalbagni G. Can Restaging Transurethral Resection of T1 Bladder Cancer Select Patients for Immediate Cystectomy? J Urol 2007;177:75-9.

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29. Dobruch J, Borówka A, Herr HW. Clinical Value of Transurethral Second Resection of Bladder Tumor: Systematic Review. Urology 2014;84:881-5.
30. Gendy R, Delprado W, Brenner P, et al. Repeat transurethral resection for non-muscle-invasive bladder cancer: a contemporary series. BJU Int 2016;117 Suppl 4:54-9.
31. Kamiya N, Suzuki H, Suyama T, et al. Clinical outcomes of second transurethral resection in non-muscle invasive high-grade bladder cancer: a retrospective, multi-institutional, collaborative study. Int J Clin Oncol 2017;22:353-8.
32. Vasdev N, Dominguez-Escrig J, Paez E, et al. The impact of early re-resection in patients with pT1 high-grade non-muscle invasive bladder cancer. Ecancermedicalscience 2012;6:269.
33. Sfakianos JP, Kim PH, Hakimi AA, et al. The Effect of Restaging Transurethral Resection on Recurrence and Progression Rates in Patients with Nonmuscle Invasive Bladder Cancer Treated with Intravesical Bacillus Calmette-Guérin. J Urol 2014;191:341-5.
34. Divrik RT, Sahin AF, Yildirim U, et al. Impact of routine second transurethral resection on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma with respect to recurrence, progression rate, and disease-specific survival: a prospective randomised clinical trial. Eur Urol 2010;58:185-90.
35. Divrik RT, Yildirim U, Zorlu F, et al. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. J Urol 2006;175:1641-4.
36. Lazica DA, Roth S, Brandt AS, et al. Second transurethral resection after Ta high-grade bladder tumor: a 4.5-year period at a single university center. Urol Int 2014;92:131-5.
37. Tae BS, Jeong CW, Kwak C, et al. Pathology in repeated transurethral resection of a bladder tumor as a risk factor for prognosis of high-risk non-muscle-invasive bladder cancer. PLoS One 2017;12:e0189354.
38. Gordon PC, Thomas F, Noon AP, et al. Long-term Outcomes from Re-resection for High-risk Non-muscle-invasive Bladder Cancer: A Potential to Rationalize Use. Eur Urol Focus 2017. [Epub ahead of print].
39. Audenet F, Retinger C, Chien C, et al. Is restaging transurethral resection necessary in patients with non-muscle invasive bladder cancer and limited lamina propria invasion? Urol Oncol 2017;35:603.e1-603.e5.
40. Angulo JC, Palou J, García-Tello A, et al. Segunda resección transuretral y pronóstico del cáncer de vejiga no músculo-invasivo de alto grado en pacientes que no reciben bacilo de Calmette-Guérin. Actas Urológicas Españolas 2014;38:164-71.
41. Naselli A, Hurle R, Paparella S, et al. Role of Restaging Transurethral Resection for T1 Non-muscle invasive Bladder Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus 2018;4:558-67.
42. Bishr M, Lattouf JB, Latour M, et al. Tumour stage on re-staging transurethral resection predicts recurrence and progression-free survival of patients with high-risk non-muscle invasive bladder cancer. Can Urol Assoc J 2014;8:E306-10.
43. Kim PH, Kent M, Zhao P, et al. The impact of smoking on pathologic response to neoadjuvant cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer. World J Urol 2014;32:453-9.
44. Hashine K, Ide T, Nakashima T, et al. Results of second transurethral resection for high-grade T1 bladder cancer. Urol Ann 2016;8:10.
45. 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.
46. 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.
47. Gaya JM, Palou J, Cosentino M, et al. La re-resección transuretral puede no ser necesaria en todos los tumores vesicales no músculo-invasivos de alto grado. Actas Urológicas Españolas 2012;36:539-44.
48. Yucel M, Hatipoglu NK, Atakanli C, et al. Is Repeat Transurethral Resection Effective and Necessary in Patients with T1 Bladder Carcinoma? Urol Int 2010;85:276-80.
49. Richterstetter M, Wullich B, Amann K, et al. The value of extended transurethral resection of bladder tumour (TURBT) in the treatment of bladder cancer. BJU Int 2012;110:E76-9.
50. Rouprêt M, Yates DR, Varinot J, et al. The presence of detrusor muscle in the pathological specimen after transurethral resection of primary pT1 bladder tumors and its relationship to operator experience. Can J Urol 2012;19:6459-64.
51. Kramer MW, Rassweiler JJ, Klein J, et al. En bloc resection of urothelium carcinoma of the bladder (EBRUC): a European multicenter study to compare safety, efficacy, and outcome of laser and electrical en bloc

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transurethral resection of bladder tumor. World J Urol 2015;33:1937-43.
52. Muto G, Collura D, Giacobbe A, et al. Thulium:yttrium-aluminum-garnet Laser for En Bloc Resection of Bladder Cancer: Clinical and Histopathologic Advantages. Urology 2014;83:851-5.
53. Hurle R, Lazzeri M, Colombo P, et al. "En Bloc" Resection of Nonmuscle Invasive Bladder Cancer: A Prospective Single-center Study. Urology 2016;90:126-30.
54. Upadhyay R, Kapoor R, Srivastava A, et al. Does En-bloc transurethral resection of bladder tumor give a better yield in terms of presence of detrusor muscle in the biopsy specimen? Indian J Urol 2012;28:275-9.
55. Naselli A, Puppo P. En Bloc Transurethral Resection of Bladder Tumors: A New Standard? J Endourol 2017;31:S20-4.
56. Migliari R, Buffardi A, Ghabin H. Thulium Laser Endoscopic En Bloc Enucleation of Nonmuscle-Invasive Bladder Cancer. J Endourol 2015;29:1258-62.
57. Mariappan P, Rai B, El-Mokadem I, et al. Real-life Experience: Early Recurrence With Hexvix Photodynamic Diagnosis-assisted Transurethral Resection of Bladder Tumour vs Good-quality White Light TURBT in New Non-muscle-invasive Bladder Cancer. Urology 2015;86:327-31.
58. Shariat SF, Milowsky M, Droller MJ. Bladder cancer in the elderly. Urol Oncol 2009;27:653-67.

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Supplementary

Table S1 Studies reporting the advantages of second look TURB for high-risk non-muscle invasive bladder cancer

Authors	Main study features					1st TURB features and BCG			Second look TURB results and outcomes							Other findings (second look TURB prognostic/clinical value /complications)
	n	Pub Year	Type	Accrual Years	Intervention	T1 Initial Pathology	1st TURB complete	BCG	Upstaging to T2 % [n]	Residual disease % [n]	Recurrence % [n]	Follow up	Progression % [n]	Follow up	CSD % [n]	
Herr *et al.*	352	2007	R	1992–2004	reTURB	T1 n=352	N	352	2.5 [9]	58.0 [203]	66.0	5 ys	35.0 [123]	5 ys	–	Second look TURB pathology predicts initial BCG response, 5-ys RFS and 5-ys PFS
																Second look TURB pathology on multivariate analysis independent predictor of BCG response and PFS
Bishr *et al.*	94	2014	R	2006–2010	reTURB	T1 n=65	N	–	14.0 [13]	52.0 [49]	–	–	–	–	–	Second look TURB T stage on multivariate analysis independent predictor of RFS and PFS
	72							83.0 [60]	–	–	64.0 [46]	32.5 mo	22.0 [16]	32.5 mo	–	
Gendy *et al.*	1,209	2016	R	2008–2013	–	–	N	–	–	–	–	3–6 mo	–	–	–	Second look TURB group higher PFS for TaHG and T1
	85				reTURB	All			9.4 [8]	77.6 [66]	47.0 [40]					–
						TaHG n=37			2.7 [1]	70.3 [26]	56.8 [21]					
						T1 n=48			14.6 [7]	83.4 [40]	39.6 [19]					
	270				No reTURB	All			–	–	83.3 [225]					
						TaHG n=167			–	–	82.5 [138]					
						T1 n=103			–	–	84.0 [87]					
Gontero *et al.**	2,451	2016	R	1990–2011			Y	100.0				5.2 ys	–	–	–	Second look TURB borderline significant positive impact on RFS, time to progression, duration of CSS when muscle not present at first TURB specimen
	935				reTURB					71.3						
	276	No muscle				T1G3 n=244			Excluded	85.9	58.3 [161]		13.8 [38]		6.9 [19]	
	624	Muscle				T1G3 n=512			Excluded	65.2	55.0 [343]		19.2 [120]		9.8 [61]	
	1,342				No reTURB											
	130	No muscle				T1G3 n=110				–	60.0 [60]		21.5 [28]		11.5 [15]	
	1,092	Muscle				T1G3 n=967				–	48.6 [531]		20.2 [221]		8.6 [94]	
Palou *et al.**	935	2018	R	1990–2011	reTURB	T1G3 n=848	Y	100.0	excluded	71.3 [667]	54.8 [512]	≥5.2 ys	17.8 [166]		9.1 [85]	Second look TURB pathology predicts recurrence and progression
																On multivariate analysis second look TURB was the most important prognostic factor for time to recurrence, progression and CSD
Lazica *et al.*	–	2013	R	2007–2011	reTURB	TaHG	N	–	5.7 [5] to T1	41.4 [36]	–	–	–	–	–	–
Sfakianos *et al.*	894	2006	R	1994–2006	reTURB	T1 n=409	N	100.0	–	55.5 [496]	61.6	5 ys	–	–	–	On multivariate analysis and improved PFS at 5 years second look TURB associated with improved RFS at 3 mo, 6 mo and 5 years
	265				No reTURB				–	–	77.2	5 ys	–	–	–	
											p<0.001					
Tae *et al.*	198	2017	R	2004–2013	reTURB	T1 n=161	N	–	–	54.0 [107]	52.0 [103]	–	9.6 [19]	–	–	On multivariate analysis second look TURB pathology (HG) significant predictor of progression and shorter time to progression
Gordon *et al.*	932	2017	R	1994–2009	–	–	N	–	–	–	–	49 mo	–	–	–	On multivariate analysis second look TURB associated with improved CSS and OS
	229				reTURB''				16.5 [38]	60.2 [138]			27.2 [126]		20.0 [46]	
	703				No reTURB''	–			–	–			10.5 [49]		22.9 [161]	
Angulo *et al.*	209	2014	R	1981–2006		T1G3 n=209	Y	0	–	–	–	5.9 ys	–	–	–	9.3% complications
	162				reTURB			0	7.4 [12]	29.8 [45]	4.6 [7]	3 mo	3.8 [6]	12 mo		6.8% minor
	47				No reTURB			0	–	–	11.4 [5]	3 mo	g	12 mo		2.5% major (1 ureteral stenosis, 2 urethral stenosis, 1 sepsis)
											P=0.06					
Hashine *et al.*	171	2016		1993–2013		T1HG n=171	N	–	–	–	–	–	–	–	–	On multivariate analysis second look TURB associated with improved OS
	79				reTURB				1.3 [1]	58.2 [46]	57.4	10 ys				
	92				No reTURB				–	–	–	–				
Kamiya *et al.*	198	2017	R	1990–2013	reTURB	T1 n=172	N	79.0	3.0 [5]	44.0 [87]	18.0 [36]	23.8 mo	8.0 [15]	23.8 mo	3.0 [5]	–
Vasdev *et al.*	486	2012	R	2001–2008	–	T1HG n=451	N					49.3 mo	–	49.3 mo	–	–
	172				reTURB			53.0 [92]	6.9 [12]	54.6 [94]	35.0	50 mo	3.3 [2]	50 mo		
	314				No reTURB			58.6 [184]	–	–	42.0	49 mo	14.4 [19]	49 mo		
											P=0.15		P=0.02			
Kim *et al.*	126	2012	RCT	2008–2009		High risk cancers	Y									Second look TURB independent prognostic factor for RFS in multivariate analysis
	63				reTURB			33.3	3.8 [2]	96.8 [61]	17.0 [8]	16 mo	2.6	16 mo	–	No complications occurred
	63				No reTURB			41.2			23.0 [46]	17.2 mo	19.9	17.2 mo	–	
											P=0.002		P>0.5			
Divrik *et al.*	210	2010	RCT	2001–2005			Y	–				66.1 mo				On multivariate analysis second look TURB associated with improved RFS
	105				reTURB	HG n=56			7.6 [8]	33.3 [35]	41.0 [37]	5 ys	7.0 [6]	5 ys	16.7 [5]	n=4 prolonged bleeding managed conservatively – n=1 epididymitis
	98				No reTURB	HG n=44					68.0 [70]	5 ys	21.0 [23]	5 ys	31.4 [35]	n=1 acute urinary retention
											P<0.001			P<0.001	P=0.038	

*, same cohort of patients.