Review Article

Treatment and management of high-grade T1 bladder cancer: what should we do after second TUR?

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Abstract

Most T1 bladder cancers are high grade and have the potential to progress to muscle invasion and extravesical dissemination. Many studies reported that ~50% of patients displayed residual tumors when a second transurethral resection was performed 2–6 weeks after the initial resection for patients who were diagnosed with T1 bladder cancer. Furthermore, muscle-invasive disease was detected by the second transurethral resection in 10–25% of those patients. Therefore, a second transurethral resection is strongly recommended for patients newly diagnosed with high-grade T1 bladder cancer in various guidelines. T1 bladder cancers are heterogeneous in terms of progression and prognosis after the second transurethral resection. Optimal management and treatment should be considered for patients with T1 bladder cancer based on the pathological findings for the second transurethral resection specimen. If the second transurethral resection reveals residual tumors, aggressive treatments based on the pathological findings should be performed. Conversely, overtreatment with respect to the tumor status should be avoided. Since the evidence of pathological diagnosis at the second transurethral resection is insufficient and many retrospective studies were carried out before the second transurethral resection era, prospective randomized studies should be conducted.

Key words: bladder cancer, high grade, T1, transurethral resection, radical cystectomy

Introduction

Bladder cancer is the seventh most common cancer in men and the 17th most common in women worldwide (1,2). Approximately 75% of patients with bladder cancer present with non-muscle-invasive disease confined to the mucosa [Ta or carcinoma in situ (CIS)] or lamina propria (T1) (3). In non-muscle-invasive bladder cancer (NMIBC), ~70% of the patients present with Ta, 20% with T1 and 10% with CIS lesions (4). Most T1 tumors are high grade (HG) and have the potential to progress to muscle invasion and extravesical dissemination (5). A long-term study of high-risk NMIBC including T1 tumors showed progression and cancer death rates as high as 53 and 34%, respectively (6). Thus T1 bladder cancers are associated with a significant risk of metastasis and death (7). The International Bladder Cancer Group defines progression of NMIBC as an increase in the T stage not only as development of T2 or greater, but also as an increase in the T stage from CIS or Ta to T1(8).

Transurethral resection of bladder tumor (TURBT) is aimed at staging Ta, T1 or CIS and removing all endoscopically visible lesions. However, many studies have reported that ~50% of patients display residual tumors when a second TUR is performed 2–6 weeks after the initial resection for patients who were diagnosed with T1 bladder cancer (Table 1) (9–16). Furthermore, muscle-invasive bladder cancer (MIBC) is detected by the second TUR in 10–25% of those patients.
(9–16). According to a meta-analysis, residual and up-staging rates at the second TUR were 47 and 24%, respectively (17). Therefore, a second TUR within 6 weeks after the primary TURBT is strongly recommended for patients newly diagnosed HG T1 bladder cancer in various guidelines (3,18–20).

With the aim of risk stratification among T1 bladder cancers, several substaging systems have been proposed (Table 2). Although many studies (21–37) reported predictive values for progression and/or survival (Table 3), these substaging systems have not been widely used in clinical practice. One of the main reasons is the difficulty in consistent and accurate assessment of TURBT tissue for the actual depth of invasion because of orientation and artifactual changes (8,38). A new substaging system discerning T1m and T1e (34) might provide accurate and reliable information on progression or survival, but it requires validation studies.

In any case, T1 bladder cancers are heterogeneous with respect to progression and prognosis after a second TUR (Fig. 1). Some tumors have the potential to progress to muscle-invasive or metastatic disease, which should be considered when deciding whether to perform aggressive treatment, e.g. radical cystectomy. On the other hand, some tumors can be completely resected by the initial TURBT, meaning that aggressive post-TUR treatment may be excessive. Although the current standard treatment for patients with HG T1 bladder cancer who have pT0 histology at the second TUR is intravesical bacillus Calmette-Guérin (BCG) therapy, there is no evidence concerning whether intravesical additional therapy is necessary for those patients (39). Thus, optimal management and treatment should be considered for patients with T1 bladder cancer based on the pathological findings for the second TUR specimen.

Table 1. Pathological results of second transurethral resection (TUR) considering residual tumor and progression to muscle-invasive disease of T1 bladder cancer at first transurethral resection of bladder tumor (TURBT).

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Residual tumor (%)</th>
<th>Muscle invasion (%)</th>
<th>Interval (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klän (9)</td>
<td>46</td>
<td>43</td>
<td>2</td>
<td>1–2</td>
</tr>
<tr>
<td>Herr (10)</td>
<td>58</td>
<td>78</td>
<td>28</td>
<td>4–6</td>
</tr>
<tr>
<td>Brauers (11)</td>
<td>42</td>
<td>62</td>
<td>5</td>
<td>4–6</td>
</tr>
<tr>
<td>Schips (12)</td>
<td>76</td>
<td>33</td>
<td>8</td>
<td>4–6</td>
</tr>
<tr>
<td>Schweibold (13)</td>
<td>136</td>
<td>52</td>
<td>10</td>
<td>4–6</td>
</tr>
<tr>
<td>Divrik (14)</td>
<td>105</td>
<td>33</td>
<td>8</td>
<td>2–6</td>
</tr>
<tr>
<td>Ali (15)</td>
<td>91</td>
<td>67</td>
<td>26</td>
<td>2–6</td>
</tr>
</tbody>
</table>

MM, muscularis mucosae.

Table 2. Substaging systems discerning T1 bladder cancer.

<table>
<thead>
<tr>
<th>Substaging</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a/T1b (21–25)</td>
<td>T1a: No invasion beyond MM</td>
</tr>
<tr>
<td></td>
<td>T1b: Invasion beyond MM</td>
</tr>
<tr>
<td>T1a/T1b (26–35)</td>
<td>T1a: Invasion above MM</td>
</tr>
<tr>
<td></td>
<td>T1b: Invasion to MM or deeper</td>
</tr>
<tr>
<td>T1a/T1b/T1c (36,37)</td>
<td>T1a: Invasion above MM</td>
</tr>
<tr>
<td></td>
<td>T1b: Invasion within MM</td>
</tr>
<tr>
<td></td>
<td>T1c: Invasion below MM</td>
</tr>
<tr>
<td>T1m/T1e (34)</td>
<td>T1m: T1-microinvasive</td>
</tr>
<tr>
<td></td>
<td>T1e: T1-extensive-invasive</td>
</tr>
</tbody>
</table>

Table 3. Impact of substaging on progression and survival

<table>
<thead>
<tr>
<th>Substaging</th>
<th>Significance in progression</th>
<th>Significance in cancer-specific survival</th>
<th>Significance in overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>T1a + b (invasion to MM) versus T1c (invasion beyond MM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a (invasion above MM) versus T1b + c (invasion to MM or deeper)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a versus T1b versus T1c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 m versus T1e</td>
<td></td>
<td></td>
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</tbody>
</table>

*Significant in multivariate analysis.
analysis that showed no statistically significant difference between BCG and MMC for progression and survival (51).

However, these recommendations were based on the results from studies carried out before the second TUR era. There is no evidence demonstrating that intravesical BCG is necessary for patients with HG T1 bladder cancer who have pT0 histology after a second TUR. It is possible that pT0 status after the second TUR carries a minimal risk for recurrence or progression and that intravesical BCG therapy is overtreatment for these patients. It takes ~2 months to complete initial intravesical BCG therapy, and adverse events such as pollakisuria, hematuria and dysuria occur in almost all patients. Furthermore, maintenance BCG may inflict more adverse events and an economic load on patients. Currently the Urologic Oncology Study Group of the Japan Clinical Oncology Group (JCOG) is conducting a multi-institutional Phase III trial to evaluate the non-inferiority in terms of recurrence-free survival (excluding Tis or Ta intravesical recurrence) of a watchful waiting arm compared with an intravesical BCG therapy arm for patients with high-grade pT1 bladder cancer who have pT0 histology after a second TUR (JCOG1019 trial, Fig. 2) (39).

**Treatment for HG T1 bladder cancer with pTis histology at second TUR**

CIS by itself is categorized a high-risk bladder cancer in stage T1 (3,19,20,50). It has been suggested to be a precursor lesion of muscle-invasive disease and concomitant CIS is considered to be a significant risk factor for a poor outcome (52). Since it is almost impossible to completely resect CIS lesions, intravesical BCG is recommended (3,18–20,50,52) and widely used in the treatment of CIS. Radical cystectomy is considered when the results of conservative treatment after BCG failure are disappointing (52).
Hurle et al. (41) examined prognostic factors in 51 patients with T1G3 bladder cancer who received intravesical BCG and reported that tumor size (≥3 cm) and CIS were associated with disease progression in multivariate analysis. Sylvester et al. (53) performed combined analysis of 194 patients with T1G3 bladder cancer from seven European Organization for Research and Treatment of Cancer trials. The investigators demonstrated that the most important prognostic factor in patients with T1G3 tumors was the presence of concomitant CIS. In that study, 1- and 5-year progression probabilities in patients with CIS were 29 and 74%, respectively, whereas those in patients without CIS were 10 and 29%, respectively. Denzinger et al. (54) examined 132 consecutive patients with initial T1G3 and no prior history of bladder cancer who completed six weekly adjuvant BCG instillations followed by TURBT. This study showed that only CIS was significantly correlated with recurrence, progression and cancer-specific death in multivariate analysis. These investigators also examined long-term outcomes of patients with T1G3 bladder cancer treated with radical cystectomy for recurrence after an initial bladder-sparing approach in another study (55). They compared the survival rates of patients treated with early versus deferred cystectomy, and demonstrated that CIS was related to lower cancer-specific survival for deferred cystectomy.

Orsola et al. (56) analyzed predictive factors of positive findings at 3 months after TURBT followed by BCG therapy for patients with HGT1 bladder cancer. The investigators showed that tumor size (>3 cm) and CIS were significantly associated with tumor persistence or early recurrence and present in 26% of the patients, although this study lacked progression and survival data. Kakiashvili et al. (57) examined the long-term results of BCG for 136 patients with HGT1 bladder cancer. The investigators reported that CIS was a significant independent predictor of recurrence but not progression. They suggested that the difference could be explained by the homogeneity of subjects since all patients in their series were treated with BCG and all tumors were primary HGT1 rather than all combinations of NMIBC. Some studies found no impact of concomitant CIS on progression or survival (42,44).

The EAU guidelines note that T1G3 associated with concurrent CIS is one of the factors of the highest-risk tumors (3), since many studies reported that concomitant CIS has a negative impact on prognosis as mentioned above. However, early radical cystectomy is overtreatment in ~50% of patients with CIS alone (58). Therefore, radical cystectomy should be offered to patients with recurrent or persistent tumors after intravesical BCG therapy (52).

**Treatment for HG T1 bladder cancer with pTa histology at second TUR**

In this situation, the tumors detected at the second TUR are non-invasive but missed at the first TURBT. This may be caused by technical problems with the first TURBT. Another possibility is the difficulty in differential diagnosis between pathological Ta and Tis.
Dalbagni et al. (59) investigated clinical outcomes of 523 patients with T1 bladder cancer who received a second TUR in a contemporary series. They compared the differences in disease-specific survival among patients with lower than T1, T1 and T2 disease at the second TUR. The survival in patients with lower than T1 was similar to that of those with T1 disease at the second TUR, whereas the patients with T2 disease had the worst disease-specific survival. The cumulative incidences of disease-specific death at 5 years were 8, 10 and 44% for patients with lower than T1, T1 and T2 disease at the second TUR, respectively. Takaoka et al. (60) conducted a multi-institutional study to determine risk factors for intravesical recurrence of HG T1 bladder cancer in the second TUR era. They retrospectively reviewed 73 patients who received a second TUR for treatment of HG T1 bladder cancer. The distribution of second TUR pathology was pT10 in 49%, pTis/a in 29%, pT1 in 18% and pT2 in 4%. Univariate and multivariate analyses showed that pTis/a at the second TUR was associated with a higher intravesical recurrence rate. Thus, the situation of T1 bladder cancers with pTa histology at the second TUR is considered to be similar to that with pTis histology at the second TUR. Therefore, intravesical BCG therapy should be indicated for HG T1 patients whose second TUR specimens display HG Ta tumors alone.

It is true that immediate cystectomy offers the best opportunity to cure HG T1 cancer with residual T1 disease found at a second TUR. However, the survival rate of those patients may be similar to those who are treated with conservative management judging from the recent literature. This means that immediate cystectomy would constitute overtreatment in some cases. Therefore, we have to select patients for whom radical cystectomy is really required just after the second TUR. Multivariate analysis by Badalato et al. (65) indicated that lymphovascular invasion (LVI) at the time of TUR was associated with recurrence or progression during follow-up after conservative management. Segal et al. (70) assessed prognostic factors for disease-worsening, defined as evidence of disease stage progression, the need for radical cystectomy or disease-specific mortality (71), in patients with HG T1 bladder cancer. Primary tumors, sessile architecture, trigonal tumor location and the use of intravesical BCG are factors associated with a worse outcome (70). Although these factors may be used to counsel patients towards immediate cystectomy, further investigations using data from patients who have received a second TUR are needed.

Treatment for HG T1 bladder cancer with pT1 histology at second TUR

In theory, T1 tumors can be completely removed by TUR. However, residual T1 tumors in second TUR specimens are associated with future muscle-invasive disease. Herr et al. (61) evaluated the relationships between the second TUR pathology and future progression of 352 patients with T1 bladder cancer on initial TURBT. Of the 92 patients with residual T1 disease at the second TUR, 82% progressed to muscle invasion within 5 years. In contrast, of the 260 patients without lamina propria invasion at the second TUR, only 19% progressed at 5 years. A multi-institutional study including 1136 patients with T1 bladder cancer who underwent radical cystectomy demonstrated that 50% of these cancers were upstaged to muscle-invasive disease after cystectomy (62). Another collaborative study (63) including 167 patients who underwent radical cystectomy for T1 G3 bladder cancer revealed that 50% of the patients were pathologically upstaged on cystectomy specimens and 28% had extravesical disease. Other contemporary series showed upstaging in the cystectomy specimen in 20–51% (55,64–68). Ark et al. (67) demonstrated that the survival rate for patients who were appropriately staged was significantly higher than for those who were understaged at the final pathology from radical cystectomy.

There are several studies (55,64,65,68,69) comparing oncological outcomes in patients with initial HG T1 bladder cancer who were treated with immediate cystectomy versus deferred cystectomy for recurrent T1 or MIBC after a bladder-sparing approach (Table 5). Many of the studies showed higher survival rates for patients undergoing immediate cystectomy than for those undergoing deferred cystectomy. Conversely, Badalato et al. (65) reported that there was no difference in cancer-specific survival between early and deferred cystectomy groups. In the comparison of immediate cystectomy versus conservative management (TUR plus intravesical therapy), the conservative management group displayed significantly better cancer-specific survival than the early cystectomy group (P = 0.012) (65). Furthermore, recent series in which second TUR was routinely performed showed no difference in survival between the immediate cystectomy versus no immediate cystectomy groups (59,66).

Treatment for HG pT1 bladder cancer with pT2 or more histology at second TUR

There is no doubt about the need to perform radical cystectomy for patients with muscle-invasive disease at the second TUR. Most of these tumors are understaged at the initial TURBT due to technical problems, and may not be large or bulky like muscle-invasive tumors that are diagnosed at the initial TURBT and/or with computed tomography or magnetic resonance imaging. The discussion on the treatment strategies for these tumors does not include whether cystectomy should be performed but whether neoadjuvant chemotherapy and/or extended lymph node dissection (LND) should be performed.

Several randomized Phase III trials (72–74) and meta-analyses (75,76) demonstrated the survival benefit of cisplatin-based neoadjuvant chemotherapy for patients with MIBC. However, whether neoadjuvant chemotherapy prolongs the survival of patients with T1 cancer at the initial TURBT and with muscle-invasive disease detected by a second TUR is unclear. Neoadjuvant chemotherapy offers potential advantages in tumor downstaging and eradication of micrometastases, so this therapy should be indicated for patients who have risk factors for locally advanced disease or nodal metastasis.

Culp et al. (77) evaluated survival and the rate of pathological upstaging of 297 patients who underwent radical cystectomy without neoadjuvant chemotherapy. The investigators defined high risk based on the clinical presence of hydrourerteronephrosis, clinical T3b–T4a disease and/or histological evidence of LVI, as well as micropapillary and neuroendocrine features on TUR. High-risk patients exhibited decreased 3-year overall survival (47 versus 65%) and decreased disease-specific survival (64 versus 84%) probabilities compared with low-risk patients (P = 0.001) (77). The investigators concluded that the presence of high-risk features identifies patients with a poor prognosis who are most likely to benefit from neoadjuvant chemotherapy (77). Ahmadi et al. (78) developed a prediction model of upstaging for patients with clinical organ-confined bladder cancer. The investigators determined predictive variables such as the clinical stage, LVI, hydronephrosis, tumor multiplicity, etc. This study presented a validated model to predict the post-cystectomy stage that might reduce pathological upstaging (78). The secondary analysis of the Southwest Oncology Group-directed intergroup study (S8710) revealed that the presence of squamous or glandular differentiation did...
not confer resistance to neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin. Thus, patients with factors such as clinical T3 or more, hydronephrosis, LVI, micropapillary or neuroendocrine features on TUR should be considered for neoadjuvant chemotherapy.

To date, there has been no publication of a prospective randomized trial concerning the clinical benefits of LND during radical cystectomy. The University of Southern California (USC) and University of Bern (UB) conducted a large retrospective study for the optimal boundaries of LND during radical cystectomy (79). The pure intrapelvic template was almost identical at the two institutions. At USC the template included removal of lymphatic tissue along the common iliac vessels, the distal vena cava/aorta to the inferior mesenteric artery (IMA) takeoff and complete dissection of the presacral space from the bifurcation of the aorta into the sacral fossa. At UB the template ended proximally at the mid-upper third of the common iliac vessels. It included the presacral region medial to the internal iliac vessels but left tissue containing the hypogastric nerves located medial to the retracted ureters and inferior to the aortic bifurcation. Although more lymph nodes were removed in patients at USC than in UB, there was no significant difference in survival between node-negative patients and node-positive patients at the two institutions (79). Therefore, LND to the level of the aortic bifurcation is considered to be the recommended boundary. Meta-analyses and systemic reviews concluded that any form of LND produces more favorable oncologic outcomes than no LND (80), and that extended LND (up to the proximal boundary of the crossing of the common iliac vessels with the ureters or the aortic bifurcation) might be superior to lesser degrees of dissection from an oncologic perspective (80–82). A Danish retrospective study (83) reported that there was no benefit of extended LND to the IMA takeoff in patients with T1−2N0 disease, whereas extended LND provided longer survival in patients with node-positive or locally advanced disease than limited dissection defined as that restricted to the obturator fossa bilaterally. In this study, the T stage was defined as highest histologically verified pT stage and pT stage of the radical cystectomy specimens (83). Considering the results of the studies mentioned above, LND to the level of the IMA takeoff is not necessary but LND including at least the obturator fossa is mandatory. Since common iliac lymph nodes are regional nodes based on a critical evaluation (84), LND to the level of the aortic bifurcation is recommended.

In summary, cisplatin-based neoadjuvant chemotherapy and pelvic LND should be considered for patients who are diagnosed as having muscle-invasive disease at the second TUR. The strategy for those patients should be according to that for MIBC, since cystectomy alone does not guarantee a cure for patients whose cancers have aggressive biologic behavior (85).

Conclusions

T1 bladder cancers are considered to be invasive with the potential to progress to muscle-invasive or metastatic disease. Second TUR is mandatory in all patients who are diagnosed with T1 bladder cancer at the initial TURBT. If the second TUR reveals residual tumors, aggressive treatments should be performed based on the pathological findings. High-quality TUR (for both the initial TURBT and second TUR) is required, which may influence the oncological outcome thereafter (86). Since the evidence for each situation of pathological diagnosis at the second TUR is insufficient and many retrospective studies were carried out before the second TUR era, prospective randomized studies should be conducted to establish the standard treatment strategies for HG T1 bladder cancers that are heterogeneous clinical entities.

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Conflict of interest statement

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