Management of pT1G3 Bladder Cancer

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**Abstract**

**Context:** Guidelines for the management of pT1G3 bladder cancer (BCa) are based on different and specific levels of evidence.

**Objective:** This review examines the clinical evidence for the management of pT1G3 BCa with an organ-preserving approach and with radical cystectomy (RC) and the risk factors involved.

**Evidence acquisition:** Data were acquired from the recent literature.

**Evidence synthesis:** The tumour biology and outcome of T1G3 bladder tumours is variable. Organ preservation is feasible in solitary tumours, with few risk factors after a second transurethral resection of bladder tumour and no evidence of residual disease. Other patients should be offered RC unless they are not fit to undergo major surgery. Risk factors include concomitant carcinoma in situ, tumour multifocality, tumour diameter >3 cm, and depth of lamina propria infiltration.

**Conclusions:** Treatment outcome may be improved through risk stratification and patient selection. In patients fit for major surgery showing multiple risk factors and at high risk for progression, RC with extended pelvic lymph node dissection should be offered. In patients with solitary tumours presenting with few risk factors and in patients not fit for major surgery, a conservative organ-preserving approach is acceptable. This risk constellation must be kept in mind for adequate counselling of patients with T1G3 disease in our everyday practice.

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The management of high-risk non–muscle-invasive bladder cancer (BCa) forces difficult decisions on the urologist taking care of these patients, especially when the tumour has invaded beyond the basal membrane but not the muscularis propria. These T1 tumours are highly malignant, with a variable and unpredictable biologic potential. Several retrospective studies have reported 5–30% of patients dying of T1G3 BCa [1].

Initial management comprises complete resection of all visible tumours, with selected biopsies of suspicious bladder areas and random biopsies of the bladder mucosa and the prostatic urethra, as these tumours are frequently associated with carcinoma in situ (CIS). A second transurethral resection of bladder tumour (TURBT) is mandatory to prevent understaging and improve treatment outcome. The understaging rates of clinical T1G3 BCa in the literature vary from 5% to 62% [2,3]. In the recent series by Denzinger et al [4], where patients who opted for immediate cystectomy did not undergo a second TURBT, upstaging at cystectomy was 30%. A second TURBT is also important, because the 3-mo early recurrence rates resulting from incomplete resection reported by the European Organisation for Research and Treatment of Cancer vary for single tumours from 3.5% to 20.6%, depending on the surgeon, indicating the difficulty in visually detecting the extent of disease during transurethral resection.
Grimm and colleagues found residual tumour in every second patient with T1G3 tumours at second resection, and Brauers et al in their series found residual tumour in 64% [5,6]. The latter were able to show that the recurrence rate was lower for patients with a negative second resection. These results were substantiated by Herr and Dalbagni, who reported that patients with residual disease 6 mo after therapy with bacillus Calmette-Guérin (BCG) have a poorer prognosis than those who are without tumour [7]. In patients undergoing immediate cystectomy, a second TURBT might not be necessary, but it should be mandatory for patients who opt for organ preservation.

In a series reported by Herr, the results of the second TURBT changed the treatment in one-third of the patients [8]. These results clearly underline the necessity for a second resection when an organ-sparing approach is being considered [9]. Similarly, photodynamic diagnosis may be an interesting approach for improving recurrence-free survival by better detection in this group of patients, as shown by Stanislaus et al [10] in a single-centre study requiring validation. Complete resection and second TURBT are followed by a single dose of intravesical chemotherapy (mitomycin C [MMC], doxorubicin, epirubicin, or thiotepa; the majority of centres use MMC [40 mg in 40 cm \(^3\) of saline] as the prophylactic chemotherapeutic agent of choice) and immunotherapy with BCG, if an organ-preserving approach is attempted [11].

A heated debate is ongoing whether organ preservation in T1G3 BCa should be undertaken. Denzinger et al [4] recently reported in a nonrandomised patient choice–based study that patients with initial high-risk T1G3 BCa have a more favourable outcome when they undergo early cystectomy as compared to those who undergo deferred cystectomy. This report has a selection bias because the group undergoing immediate cystectomy included patients who might have done well with an organ preservation approach, thus improving the overall outcome results, whereas the group undergoing deferred cystectomy included only patients who did not respond to a conservative strategy, representing a negative selection. The more favourable outcome in this study is therefore not astonishing, and this is also true for the results of large cystectomy series, where patients with pT1G3 disease underwent early or immediate cystectomy.

Shahin and colleagues, looking at 153 patients with primary T1G3 tumours, found that intravesical BCG therapy prolongs the time to recurrence and cystectomy but does not ultimately influence the biologic outcome [12]. They proposed the “rule of 30”: 30% of patients will never recur, 30% require deferred cystectomy, and 30% will die of metastasis. These findings show that there is a subpopulation that will never recur and might be managed with an organ preservation approach and another in which immediate, early cystectomy might be worthwhile.

Thus, radical cystectomy (RC) as well as TURBT, with a second resection followed by BCG, are both acceptable primary therapies for a high-grade T1 transitional cell carcinoma (TCC). Both options should be discussed in detail with the patient. For those patients who prefer initial organ preservation, they must clearly understand the lifetime risk of recurrence and progression and the need for lifelong close and regular follow-up, as recurrences may occur many years after the initial tumour [5,13].

In terms of tumour control, RC removes a large portion of the urothelium at risk of recurrence, such as the distal ureters and prostatic urethra as well as the urinary bladder, in the course of surgery. For those considering RC, they should be aware of the implications on quality of life (QoL) as well as the morbidity associated with this major operative procedure. Mortality of this procedure has significantly declined over the past decades to <2% in larger reported series; however, the morbidity still ranges between 20% and 30% [14–17]. For younger men and women, issues such as sexual function are relevant and need to be discussed. In addition, urinary diversion has an impact on QoL. For those receiving an ileal conduit, this change in function may present a psychological problem. The use of an orthotopic neobladder in this context clearly has improved the QoL of these patients. In younger patients, nerve-sparing and, in select cases, prostate-sparing surgery to improve functional outcome in terms of continence and sexual function might be considered [18].

T1G3 BCa is a potentially lethal disease, and aggressive treatment should be considered and discussed with the patient when risk factors for progressive disease are present. Patient risk stratification and selection can help improve treatment outcome. Several attempts have been undertaken to differentiate T1G3 tumours according to pathologic stage and other factors, such as tumour size, multifocality, presence of concomitant CIS, and depth of invasion into the lamina propria. A large tumour size increases the risk of undetected infiltration of the lamina propria, especially in cases where no second resection has been performed. Cheng et al demonstrated that tumours >1 cm in diameter fared less well than smaller tumours [19]. The depth of tumour infiltration into the lamina propria also had an important impact on survival in patients with T1G3 tumours in the same series [19]. The more the lamina propria, which contains blood and lymphatic vessels, is invaded, the higher the chance of early dissemination, as substantiated by a 10–20% incidence of lymph node involvement in this population in the literature.

The reasons for a poorer outcome in patients with multifocal disease are multiple. Multifocal tumours tend to be underestimated in terms of pathologic stage, the chances of complete resection decreases with the number of tumours, and multifocality indicates the susceptibility of the entire urothelium to develop tumours (field effect), which suggests a strong need for close follow-up of the urethra and the upper urinary tract after cystectomy and the bladder for patients treated with an organ-preserving approach. Denzinger et al [4] and others reported that the presence of concomitant CIS is a poor prognostic factor [20]. CIS is often not only present in the bladder of patients with TCC but may also be found in extravesical locations, such as the distal ureters and the prostatic urethra, and, if untreated or not actively sought, may account for a number of patients with progressive and recurrent disease, despite therapy in
curative intent. Therefore, it is of utmost importance to evaluate the upper urinary tract, the prostate, and the urethra for CIS in these patients on a regular basis, especially in those not responding to intravesical immune modulatory treatment with BCG for CIS of the bladder. BCG requires contact with the urothelium to be effective; thus, extravesical CIS is not treated adequately when BCG is not applied to the upper urinary tract or the urethra directly. Further risk factors that have been reported are the micropapillary variant of TCC and tumours with lymphovascular invasion.

Recent reviews have emphasised the use of BCG and suggested that maintenance BCG may decrease progression rates; however, many of the studies have a follow-up of <5 yr. The overall progression is in the range of 10–20%, but varies from 5% to 35% [21–23]. Herr reported that after 15 yr of follow-up, one-half of patients progress to a muscle-invasive tumour, and approximately one-third of the patients die of BCa [24].

The response to intravesical therapy is an important predictive factor. Soloway and colleagues suggest a second course of BCG if the recurrent lesion is Ta or CIS and cystectomy for recurrent T1G3 tumours [25]. With this approach, the Memorial Sloan-Kettering Cancer Centre group found a 71% cumulative incidence of progression to muscle-invasive disease at 5 yr in a group of 214 patients with high-risk BCa who experienced a stage T1G3 recurrence [26]. Patients treated with a second course of BCG died of progressive disease in 48% of cases, whereas patients treated with delayed cystectomy died in 31% of cases, stressing the need for aggressive treatment for recurrent disease after BCG therapy.

Considering the factors discussed, treatment outcome may be improved through risk stratification and patient selection. In patients fit for major surgery showing multiple risk factors and at high risk for progression, few surgeons will propose an organ preservation approach. This risk constellation must be kept in mind for adequate counselling of patients with T1G3 disease in our everyday practice.

Conflicts of interest

The authors have nothing to disclose.

Funding support

None.

References


