The optimal management of T1 high-grade bladder cancer

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Abstract

Stage T1Hg bladder cancer should be considered an aggressive and potentially lethal disease. The importance of initial re-resection to identify unrecognized muscle-invasive disease is significant. Most patients with high-risk disease are candidates for initial bladder salvage with intravesical bacillus Calmette-Guerin vaccine for immunotherapy, a procedure with a high survival rate; however, failure of the procedure may result in a guarded prognosis. Even after apparent success, patients should be informed of the risks of the disease progressing to muscle-invasive or metastatic disease and the need for vigilant monitoring. Despite optimal management, a significant number of patients relapse or progress to invasive disease requiring cystectomy. This review provides insight into the optimal management of T1 high-grade bladder cancer.

Can Urol Assoc J 2009;3(Suppl4):S188-92

Introduction

Approximately 70% of all newly diagnosed bladder tumours are non-muscle invasive bladder cancers (NMIBC), including stage Ta, stage T1 and carcinoma in situ (CIS). Non-muscle invasive bladder cancers exist on a continuum of risk in patients with T1 high-grade (T1Hg) bladder cancer at the aggressive end of the spectrum. Following transurethral resection alone, T1Hg bladder cancer has a 69% to 80% recurrence rate and a 33% to 48% chance of progression to muscle-invasive disease.[1-4] This review provides insight into the optimal management of T1Hg bladder cancer.

Initial resection

Optimal management of T1Hg bladder cancer begins with complete initial transurethral resection of the bladder tumour (TURBT). A rectal or bimanual exam under anaesthesia is recommended on presentation of TURBT to evaluate any local extension. Following initial TURBT, attempts should be made to provide complete tumour resection including muscle in the specimen. To avoid perforation, you must follow the contour of the bladder. Anaesthetic paralysis or obturator nerve block while resecting an area near the obturator nerve may be helpful in preventing adductor contraction and potential bladder perforation. Sending separate pathology specimens from the superficial tumour and deeper bites of the muscle may assist pathologists in accurately staging the depth of invasion. An immediate postoperative dose of intravesical chemotherapy (mitomycin 40 mg in 40 cc water) has been reported to decrease the frequency of recurrence in low- and high-risk patients by 39% in a meta-analysis of 7 randomized trials that included 1476 patients.[5] Even among patients scheduled to receive bacillus Calmette-Guerin (BCG) vaccine, there may be some benefit to a single dose of perioperative chemotherapy; this approach, however, remains controversial.[6,7]

Pathology

T1 bladder cancer represents 5% to 20% of NMIBC[3,8,9] and is defined as an invasion into the lamina propria without invasion into the muscularis propria. The 2004 World Health Organization pathology guidelines recommend a conversion from the previous classification of grade G1, G2 or G3 to that of low- or high-grade papillary urothelial carcinoma.[10] Pathology reports should identify whether muscle tissue is present in the resected specimen. One study described that a pathology report of a repeat resection of T1 disease found the incidence of understaging was only 14% when muscle tissue was present compared to 49% when muscle tissue was absent in the initial specimen.[11] It is recommended that pathologists report the extensiveness of T1 disease since some studies have reported that focal lamina propria invasion may present fewer risks than extensive involvement.[12] While understaging remains problematic, overstaging of T1 disease in pathology reports has been described; about 25% to 35% of cases were found to be stage Ta disease when reviewed by a second pathologist.[6,13,14] This is significant to the discussion of cystectomy for treatment of stage T1 disease.

Repeat resection

Understaging is significant in patients with a recent diagnosis of T1Hg bladder cancer. The standard of care has progressed to mandatory second resection (restaging TURBT) in cases of T1Hg bladder cancer. The recommended timeframe for repeat resection is about 4 weeks for patients with T1Hg bladder cancer. At time of re-resection, 45% to 76% of patients

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demonstrate residual bladder cancer and 29% to 40% are upstaged to muscle-invasive disease.[10,15,16] One study of patients with stage T1 disease that underwent immediate cystectomy following repeat TURBT found that 2 of the 15 patients (13%) had muscle-invasive disease.[17] Repeat resection may also provide prognostic information. In one study, patients diagnosed with less than T1 disease had a progression rate of 14% while those with residual T1 disease had a 76% progression rate following repeat resection.[11] Repeat resection also improves the efficacy of intravesical therapy.[18,19]

Even when no residual disease is visible at repeat resection, the prior resection base should be biopsied. Although not mentioned in the guidelines by the European Urology Association, American Urological Association or even the National Comprehensive Cancer Network, random bladder biopsies can be performed in other portions of the bladder to assess for concomitant CIS. The bladder biopsy is particularly useful in the event of positive cytology.[20] One study reported the only precystectomy prognostic predictor of recurrence was the presence of concomitant CIS.[21] The actual therapeutic benefit of regimented random biopsies during restaging TURBT is, however, probably minimal because these patients should be considered high risk by that point and the presence of CIS would not alter management of the disease.

Patient counselling

Counselling patients with T1Hg bladder cancer on their treatment options (bladder-sparing intravesical therapy versus cystectomy) is an extensive and delicate process. Factoring in risk of recurrence and progression, patient age and medical comorbidities that predict life expectancy and quality of life is one of the most daunting clinical challenges facing urologists.[22] Patients should be thoroughly informed about the risks of progression to muscle-invasive disease or development of metastases. Patients must be instructed that vigilant surveillance of symptoms is imperative when receiving conservative therapy.

The worst scenario for patients with T1Hg bladder cancer is progression to an unresectable or metastatic stage during intravesical therapy. T1Hg bladder cancer progresses to muscle-invasive or metastatic disease at a rate of 30% to 50% after 5 years.[2,23] As a result, some studies advocate initial cystectomy based on the perceived acceptable morbidity and a 5-year disease-specific survival rate of 80% to 90%.[24-28]

However, the paucity of effective conservative treatment alternatives for stage T1 disease may be misinterpreted as an immediate mortality risk in patients who continue to exhibit organ-confined disease. As we will discuss later, an initial trial of BCG rather than immediate cystectomy appears justified in almost all initial T1Hg cases without undue risk, since progression within the first six months is rare (less than 4%).[9] As previously discussed, a pathology report that overstages T1 disease could result in some patients undergoing cystectomy for stage Ta disease. Furthermore, the unconvincing results associated with delayed cystectomy do not account for the successful patients who avoided surgery. The risks associated with over-treatment of 50% to 70% of patients with unnecessary cystectomy appear too great to warrant cystectomy as standard practice; however, the issue remains heavily debated. There are no prospective studies that demonstrate that early cystectomy has a survival benefit[29] and there are obvious quality-of-life issues associated with performing unnecessary cystectomies.

Indications for immediate cystectomy in T1Hg disease do exist. They include extensive unresectable disease, diverticular disease, associated hydronephrosis, lymphovascular invasion, prostatic stromal or ductal involvement or variant histology (squamous cell, adenocarcinoma, micropapillary, small cells that require chemotherapy first). Some patients with T1Hg disease and with no concomitant CIS may be candidates for partial cystectomy. Relative indications for cystectomy include multifocal disease, associated CIS, T1 disease on repeat resection, deep T1 disease abutting the muscle and poor patient compliance. The presence of tumours that are greater than 3 cm, their multifocality and the presence of CIS have been reported as negatively prognostic.[30]

Intravesical immunotherapy

The cornerstone of early conservative treatment of T1Hg bladder cancer is intravesical immunotherapy with BCG. Ideally, intravesical therapy could safely eradicate residual tumour cells and prevent tumour recurrence, thereby averting the serious consequences of progression to muscle invasion or metastatic disease. The BCG vaccine remains the most powerful weapon in the arsenal of topical therapies against bladder cancer and has been the mainstay of adjuvant therapy since its antitumour effects were first described by Morales and colleagues in 1976.[31] Bacille Calmette-Guérin antitumour therapy appears to act via cell-mediated Th1 immune response and local influx of inflammatory cells. Multiple studies of intravesical BCG immunotherapy in T1Hg bladder cancer have reported a disease-specific survival rate of 85% to 90%, a decrease in recurrence rates of 35% to 45% and a progression rate of 15% to 25%. Disease progression with transurethral resection (TUR) alone provides a recurrence rate of 69% to 80% and a 33% to 48% chance of progression (Table 1). Other agents, such as mitomycin, may be appropriate first-line therapy in low- to intermediate-risk patients, but BCG remains the preferred agent for T1Hg disease.

Bacillus Calmette-Guerin therapy is typically administered 3 to 4 weeks following repeat tumour resection with an induction course of 6 weekly treatments. Dosage, timing and duration of intravesical treatment were based on prior study regimens that were initially and arbitrarily developed but appeared to be effective.[31] Bacille Calmette-Guérin therapy was avoided in the presence of gross hematuria,

Table 1. Published results of BCG treatment for T1 G3 bladder cancer

Author	No. patients	Follow-up, mos.	Recurrence, %	Progression, %	Disease-specific survival rate, %
Pfister, 1995[49]	26	54	50	27	92
Mack, 1995[50]	32	57	29	17	100
Pansadoro, 1995[51]	64	42	28	12	98
Pansadoro, 2002[52]	81	76	33	15	94
Hurle, 1996[53]	51	33	45	14	N/A
Hurle, 1999[48]	51	85	N/A	18	86
Lebret, 1998[54]	35	45	43	20	94
Gohji, 1999[55]	45	63	36	4	100
Brake, 2000[56]	44	43	27	16	89
Patard, 2001[57]	50	65	52	22	86
Kulkarni, 2002[58]	69	48	46	12	94
Griffiths, 2002[59]	75	41	N/A	49	59
Bogdanovic, 2002[60]	43	53	28	16	95
Peyromaure, 2003[61]	57	53	42	23	88
Shahin, 2003[62]	92	64	70	33	77
Cheng, 2004[63]	36	46	44	25	86
Weighted totals	800	56	43%	22%	88%

N/A = not available; BCG = bacillus Calmette-Guérin.

urinary tract infection and in the presence of catheter trauma because of the inherent risks of BCG dissemination. Restaging was performed as discussed below. Administration of maintenance intravesical BCG therapy is essential. In a randomized study, Lamm and colleagues reported a complete response in 87% of patients who received maintenance intravesical BCG therapy compared to 57% in the group without maintenance.[32] The maintenance therapy regimen was initiated at 3 months after induction and administered at 3, 6, 12, 18, 24, 30 and 36 months. A meta-analysis reported that administration of BCG decreased the risk of progression to 9.8% compared to 13.8% in the control group, but only when accompanied with maintenance BCG therapy.[33] There are limitations to BCG therapy since about 20% of patients are BCG intolerant and unable to complete maintenance therapy because of unpleasant local side effects.[34] Decreasing the BCG dose can enable therapy to continue in many of these cases.

Initial results on the administration of electromotive mitomycin C, which applies an intravesical electrical current, have been reported. A randomized study of BCG alone versus sequential BCG plus electromotive mitomycin C in patients with T1 bladder cancer found lower recurrence, progression and disease-specific mortality in patients who received electromotive mitomycin C.[35] However, further data are required before electromotive mitomycin C can be fully endorsed.

Restaging

A dedicated plan is essential for early reassessment after therapy. To reduce the risk of missing a high-grade recurrence after an initial induction course of BCG, restaging should be performed under aesthesia in all T1Hg bladder cancer patients after immunotherapy. In patients who had not received prior intravenous contrast imaging, a computed tomography (CT) urogram should be performed to evaluate filling defects. Operative restaging included evaluation of both the bladder and upper tracts. The bladder should be inspected and 5 random bladder biopsies taken in a stellate manner (trigone, base, dome and both lateral side walls) in addition to biopsies of suspicious areas. In cases of positive cytology without apparent bladder lesion, the upper tracts should be evaluated with urethral washings and retrograde pyelograms since CIS may not be evident on contrast imaging or even ureteroscopy. An important component of a complete evaluation is to obtain a separately labelled biopsy from the prostatic urethra since it can represent a sanctuary site for urothelial carcinoma. Other studies do not advocate the need for bladder biopsies under anaesthesia but instead recommend cystoscopy combined with cytology.[36]

Surveillance cystoscopy

Patients with a history of T1Hg bladder cancer require close surveillance cystoscopy: typically every 3 months for 2 years

from the time of the index tumour, then every 6 months for 2 years in recurrence-free patients. Most tumour recurrences occur within the first year. Cytology in combination with cystoscopy is a valuable tool for following T1Hg bladder cancer and, in this setting, demonstrates a sensitivity and specificity of 50% to 60%.[36] Abnormal cytology in the absence of a bladder lesion requires a re-evaluation as previously described. Other tests, such as florescence in situ hybridization, have shown promise but require further study.[37]

Recurrent disease

In patients with high-risk NMIBC, there is a consistent 30% to 35% initial treatment failure rate and about 50% of patients relapse at 5 years after treatment.[32,33,38] Beyond 5 years, a consistent but slower failure rate of 4% has been observed and nearly 90% recur by 15 years.[39] When patients proceed to a second course of BCG, long-term success rates average 35% (range 20% to 51%).[40] It is important to note that the sooner the relapse, the more likely the disease will be life-threatening.[39] In cases of recurrent T1Hg bladder cancer, radical cystectomy is strongly recommended. A recent multicentre review of cystectomy patients with T1Hg bladder cancer, before the era of standard re-resection, reported positive nodes in 18% of patients with a subsequent disease recurrence rate of 29% and a bladder cancer mortality rate of 19%.[21] The only predictor of precystectomy recurrence and survival was the presence of CIS, not the incidence of prior intravesical therapy or time from TUR to cystectomy.

Patients with a diagnosis of less than stage T1 who do not respond favourably to BCG therapy may be candidates for salvage intravesical therapy. A multicentre trial of patients with recurrent T1 and lack of response to BCG therapy and treated with reduced-dose BCG plus interferon-alpha (50 million units) reported a disease-free rate of 45% at 24 months.[41] Study subjects received BCG combined with interferon-alpha for salvage (and induction) based on in vitro evidence that this combination may have a synergistic effect on immune response. Other combinations of intravesical agents are currently being evaluated.[42,43]

Some patients that are candidates for cystectomy are not suitable for radical surgery because of the presence of comorbid medical illnesses or because they refuse surgery even after extended discussion of the risks. In these circumstances, alternative strategies are available but with a guarded success rate. These strategies include further salvage intravesical therapy, combination aggressive TURBT and chemotherapy or radiation. Limited studies show varying results.[44-47]

Disease outside the bladder

Patients with T1Hg bladder cancer are also at risk of developing tumours at sites outside the bladder vault. In patients with accompanying multifocal CIS, urothelial carcinoma outside the bladder in sites such as the upper tracts and prostatic urethra may occur in 10% to 20% of cases.[1,48] Upper tract abnormalities are identified as a filling defect on delayed images of a CT urogram or intravenous pyelogram. The upper tracts and prostatic urethra should also be examined when voided or when bladder-wash cytology is positive for high-grade urothelial cancer. Evaluation of abnormal cytology should be performed similarly to the restaging process previously described. Monitoring of the upper tract in patients with a history of T1Hg bladder cancer is recommended at least once every 1 to 2 years.

Conclusion

Stage T1Hg bladder cancer should be considered an aggressive and potentially lethal disease. The importance of initial re-resection to identify unrecognized muscle-invasive disease is significant. Most patients with high-risk disease are candidates for initial bladder salvage with intravesical BCG, a procedure with a high survival rate; however, failure of the procedure may result in a guarded prognosis. Even with apparent success, patients must be informed of the risks of disease progression to muscle-invasive or metastatic disease and the necessity of vigorous monitoring. Despite optimal management, a significant number of patients will relapse or progress to invasive disease and require cystectomy.

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Competing interests: None declared.

This paper has been peer-reviewed.

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