ACTA SCIENTIFIC CANCER BIOLOGY

Volume 2 Issue 10 December 2018

Review Article

Management Strategies for T1 High Grade Bladder Cancer

Anish J Jain, Pamela W Coleman and Adam R Metwalli*

Division of Urology, Department of Surgery, Howard University Hospital, Washington, DC, United States of America

***Corresponding Author:** Adam R Metwalli, Professor and Chief, Division of Urology, Department of Surgery, Howard University Hospital, Director of Urologic Oncology, Howard University Cancer Center, Washington, DC, United States of America.

Received: October 16, 2018; **Published:** November 22, 2018

Abstract

The standard of care for T1 High Grade (T1HG) bladder cancer currently involves transurethral resections of bladder tumor (TURBT) as well as Bacillus Calmette-Guerin Therapy (BCG Therapy). However, T1HG disease presents many unique challenges that may influence treating physicians to pursue other treatment options instead of the more conservative, bladder sparing treatment with BCG Therapy. These other treatment options include chemoradiation therapy (CRT), partial cystectomy, and radical cystectomy (RC). Furthermore, there several clinical factors (response or lack thereof to BCG therapy), pathological factors (tumor characteristics, histology, lymphovascular invasion), and demographics (age, sex) that can affect the efficacy of certain treatment plans. Thus it is essential consider said factors when selecting treatment plans for T1HG patients.

Keywords: Urothelial Carcinoma of the Bladder; Non-muscle Invasive Bladder Cancer; T1 High Grade Bladder Cancer; Radical Cystectomy; Bacillus Calmette-Guerin Therapy; Transurethral Resection of Bladder Tumor

Introduction

Bladder cancer is the 9th most common cancer worldwide, with the most common cell type being Urothelial Cancer of the Bladder (UCB) [1]. UCB can be described as Non-Muscle Invasive Bladder Cancer (NMIBC), which accounts for 70 - 80% of cases, or Muscle Invasive Bladder Cancer (MIBC), which accounts for the other 20 - 30% of cases. While MIBC has a worse prognosis, NIMBC remains troublesome due to its nearly 50% recurrence rate and 10 - 30% progression rate [2].

NIMBC includes tumors staged as Ta, T1, and CIS (Carcinoma In Situ). T1 disease, which invades the lamina propria, has the poorest prognosis of all NIMBC due to the increased rate of recurrence and progression to MIBC. In fact, 20% of High Grade T1 (T1HG) progresses to MIBC within 5 years [3,4].

Standard management of T1HG

Most bladder cancers are initially treated, diagnosed, and staged via a Transurethral Resection of Bladder Tumor (TURBT). An urologist will conduct the TURBT in order to gather specimens to be used by pathologists to diagnose and stage the patient's disease. If patients are diagnosed with a T1HG, a repeat TURBT is recommended within 2 to 6 weeks after the initial TURBT in order to provide more accurate staging information, as persistent tumor can be found in 33 - 55% of second TURBTs, as well as decrease the tumor recurrence rate, compared to treatment with only one TURBT [5-7]. It is also important to note that if tumor is located on the trigone or bladder neck, then biopsy of the prostatic urethra is recommended due to the high incidence of CIS in the prostatic urethra and duct [8].

The current standard treatment for high risk NIMBC, including T1HG, includes adjuvant Intravesical Immunotherapy with Bacillus Calmette-Guerin (BCG Therapy). The current recommendation is a six week induction course followed by a three weekly treatments at months 3, 6, 12, 18, 24, 30 and 16. Several studies have established the therapeutic effect of BCG in T1HG and its effectiveness in preventing recurrence [9-11]. This conservative, bladder-sparing approach is highly preferred as less than 5% of patients undergo immediate radical cystectomy (RC) in routine practice [12].

However, intravesical BCG therapy does not prevent all patients from progression to MIBC and there are several potentially systemic and local side effects associated with BCG therapy [9,13]. Notably, the 5 year Cancer Specific Survival (CSS) of patients undergoing the conservative treatment with BCG therapy was only 52% - 67%, much lower than the 83% - 90% CSS of patients treated with immediate RC. In addition, RC results in a reduced rate of recurrence, progression, and metastasis compared to BCG Therapy [14,15]. Yet, despite the survival benefits of RC, it remains a highly complex surgery which severely affects a patient's lifestyle. About 30% - 50% of patients experience perioperative or long-term complications, and the risk of mortality from RC is between 2 - 9% [16,17].

Thus, while it increased application of immediate RC in T1HG patients would likely reduce progression to MIBC and improve overall survival rates, immediate RC would also negatively impact many patients' quality of life due to the high morbidity of this operation. Several clinical and pathological features must be evaluated when considering bladder sparing BCG therapy or an immediate RC. These factors are clinical such as initial response to induction BCG, demographics such as age and female sex, and pathological including tumor size, multifocality, histology, and presence of lymphovascular invasion.

Clinical factors for consideration in T1HG management

Evidence of tumor recurrence or persistence at the time of the follow up cystoscopy after initial TURBT and certainly after induction BCG is a strong indicator of T1HG disease progression. Patients who are classified as BCG unresponsive demonstrate persistent tumor following BCG induction and/or early high-grade disease recurrence despite adequate BCG Therapy within < 6 months. These patients should be offered RC as treatment for their T1HG disease [18,19].

In addition, a subset of patients are considered BCG intolerant due to the development of severe local or systemic side effects forcing discontinuation of the therapy. These patients can be treated with intravesical chemotherapy which reduces the risk of recurrence, but not the risk of progression [20]. Thus, BCG intolerant patients suffering from T1HG disease should also be offered early RC.

Female Sex has also been shown to be a negative prognostic factor in T1HG disease. Women have an increased rate of recurrence and progression in addition to a decreased response to standard BCG therapy. However, the biological mechanisms behind the sex difference are not well understood and there are potentially several confounding variables [21,22]. Thus, patient sex is currently not a key factor in treatment planning for T1HG disease, but may prove to be in the future upon greater understanding of said biological mechanisms.

Patient age is a relevant factor in management T1HG disease particularly with respect to the morbidity and mortality of treatment options. Older T1HG patients do have an increased risk of mortality from UCB and a diminished response to BCG therapy, which are attributed to increased aggressiveness of the UCB and decreased immune response in old age respectively [3,23-25]. Given these data, RC might be a preferred option in elderly patients, yet the risks of morbidity and mortality after RC are significantly higher in older patients [26]. Conversely, younger patients tend to tolerate the morbidity of this operation better than older patients and RC should be offered early to younger patients when it is indicated.

An alternative to RC for patient with MIBC or NIMBC refractory to intravesical therapy is radiation therapy with concomitant radiosensitizing chemotherapy. This is rarely employed for T1 stage disease, despite well-documented success in T2 and higher stage UCB [27]. Given these data, some researchers contend that chemoradiation therapy (CRT) should be considered as a treatment option for T1HG UCB [28]. In MIBC, CRT has been shown to have lower morbidity and major complication rates than RC [29]. However, at this time, CRT is not part of the treatment algorithm for T1HG UCB and NIMBC in general.

Pathologic factors for consideration in T1HG management

Tumor size and location, as determined via TURBT and/or cystoscopy, can impact the difficulty of tumor treatment and disease prognosis. Martin-Doyle., *et al*. conducted a large meta-analysis which correlated larger tumors with increased risk of recurrence and progression [3]. T1HG patients with large tumors, and other poor prognostic factors, should be considered for early radical cystectomy, especially if tumors are located in sites potentially limiting resection. Understaging of tumor at sites such as the dome is

more likely due to fear of deep resection causing perforation. In very select patients with solitary tumors at locations difficult to resect transurethrally, a partial cystectomy may be an alternative treatment option, unless other risk factors or findings indicate a more aggressive approach, namely RC [26,30].

Multifocality of UCB disease is associated with significantly shorter time to recurrence of disease. However multifocality does not appear to substantially increase the risk of progression nor decrease CSS [31]. Thus multifocality alone is not compelling enough to consider immediate RC as treatment in a T1HG patient, but patients with tumor multifocality in combination with other risk factors may benefit from immediate RC [26].

Kitamura and Kakehi suggest that optimal management strategies for T1HG patient should be based on pathological findings from the follow up TURBT [32]. As mentioned previously, a follow up TURBT should be performed 2 - 6 weeks after the initial TURBT in patients with T1HG disease. In 27 - 82% of cases, residual disease has been found in the follow up TURBT, and the likelihood of having MIBC on follow up TURBT is about 2 - 30% [33,34]. Patients with T0 disease on follow up TURBT can undergo/continue BCG therapy or simply observation, while those with Ta are strongly recommended to undergo/continue BCG therapy. Patients who are upstaged to T2 disease on follow up TURBT should undergo RC. Patients with residual high volume T1HG disease are at increased risk of recurrence and progression and they should also be considered for immediate RC [26,35].

Concomitant CIS in patients with T1HG disease is considered a major determinant in treatment with early RC. It is associated with markedly increased risk of recurrence and progression. One study found that the 5 year risk of progression in patients with concomitant CIS was 74%, compared to only 29% in those without [36]. Furthermore, the 7-year CSS with concomitant CIS is 58%, versus 87% in the absence of concomitant CIS [3]. Due to the risks associated with concomitant CIS in T1HG, it may be beneficial to perform random biopsies to ensure absence of CIS, specifically during the follow up TURBT. If concomitant CIS is present in patients with T1HG disease, then early RC should be strongly considered for treatment [26,35].

UCB is the most common histological variant of bladder cancer, representing more than 90% of all cases of bladder cancer. However there are several other variants which have worse prognoses and decreased or total lack of responsiveness to BCG therapy [37]. Common variants include squamous cell (2.4% of bladder cancer cases), adenocarcinoma (1.7%), neuroendocrine (1.4%), and micropapillary (0.3%) [35]. Generally, T1HG patients with these variant histologies should be counseled regarding immediate RC [26].

Lymphovascular Invasion (LVI) is present in 10 - 36% of patients with T1 UCB and has been found significant in identifying T1HG patients at risk for lymph node metastasis [37,38]. Furthermore the progression free survival in patients with LVI versus those without LVI is markedly reduced, (66% vs85% respectively) [39]. Therefore, immediate RC should also be considered in T1HG patients with LVI, particularly when identified in combination with other significant risk factors.

Substaging of T1HG UCB in regards to depth of invasion is becoming increasingly popular and may become part of routine clinical practice in the future. Substaging of T1HG focuses on determining if there is microscopic (T1m) or extensive (T1e) invasion of the lamina propria [40]. It is a significant differentiation as T1e disease is more likely to be understaged during TURBT. The clinical application to sub-staging of T1HG tumors still needs validation in larger studies, but patients found to have T1e disease should at least be considered for RC [41].

Conclusion

The current standard treatment for T1HG UCB involves an initial and repeat TURBT for staging and diagnosis, induction and maintenance BCG therapy, with long term surveillance cystoscopy to detect residual and recurrent tumor. This conservative, bladder-sparing treatment is often used and is effective in most patients. However, significant clinical and pathologic factors can influence the effectiveness of intravesical therapy and serve as indications for more aggressive treatment strategies. In highly selected T1HG patients, partial cystectomy may be an alternative surgical approach if all other risk factors indicating need for a RC have been eliminated. The primary features that are indications for early RC in patients with T1HG disease include BCG unresponsiveness, BCG in-

tolerance, concomitant CIS, variant histology, LVI, T1e disease, and residual T1HG disease or upstaged disease on follow up TURBT. Age is another important factor in the consideration of RC due to the increased risk of mortality and morbidity associated with the operation in old age, although older patients tend to have more aggressive UCB and reduced effectiveness of BCG therapy. The role of CRT in this patient population is investigational at this time. Thus RC is often reserved for younger patients presenting with the risk factors mentioned previously. Currently T1HG UCB continues to present a complex challenge for clinicians and optimal treatment strategies for each individual patient must be personalized.

Bibliography

1. Oh CM., *et al*. "Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2013". *Cancer Research and Treatment* 48.2 (2016): 436-450.

2. Sylvester RJ., *et al*. "Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials". *European Urology* 49.3 (2006): 466-465.

3. Martin-Doyle W., *et al*. "Improving selection criteria for early cystectomy in high-grade t1 bladder cancer a meta-analysis of 15,215 patients". *Journal of Clinical Oncology* 33.6 (2015): 643-650.

4. Chalasani V., *et al.* "Radical Cystectomy for the treatment of T1 bladder cancer: the Canadian Bladder Cancer Network Experience". *Canadian Urological Association Journal* 5.2 (2011): 83-87.

5. Jahnson S., *et al*. "Results of second-look resection after primary resection of T1 tumour of the urinary bladder". *Scandinavian Journal of Urology and Nephrology* 39.3 (2005): 206-210.

6. Vasdev N., *et al*. "The impact of early re-resection in patients with pT1 high-grade non-muscle invasive bladder cancer". *Ecancermedicalscience* 6 (2012): 269.

7. Kim W., *et al*. "Value of immediate second resection of the tumor bed to improve the effectiveness of transurethral resection of bladder tumor". *Journal of Endourology* 26.8 (2012): 1059-1064.

8. Mungan MU., *et al*. "Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder". *European Urology* 48.5 (2005): 760-763.

9. Sylvester RJ., *et al*. "Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials". *Journal of Urology* 168.5 (2002): 1964-1970.

10. Shelley MD., *et al*. "Intravesical bacillus Calmette-Guérin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials". *BJU International* 93.4 (2004): 485-490.

11. Böhle A and Bock PR. "Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: formal metaanalysis of comparative studies on tumor progression". *Urology* 63.4 (2004): 682-686.

12. Canter D., *et al.* "Use of radical cystectomy as initial therapy for the treatment of high grade T1 urothelial carcinoma of the bladder: a SEER database analysis". *Urologic Oncology* 31.6 (2013): 866-870.

13. Malmström PU., *et al*. "An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer". *European Urology* 56.2 (2009): 247-256.

14. Denzinger S., *et al. "*Early versus deferred cystectomy for initial high risk pT1G3 urothelial carcinoma of the bladder: do risk factors define feasibility of bladder sparing approach?" *European Urology* 53.1 (2008): 146-152.

15. Montogomery JS., *et al*. "T1 bladder cancer: advocating early cystectomy to improve oncologic control". *Urologic Oncology* 28.5 (2010): 466-468.

16. Hautmann RE., *et al*. "Lessons learned from 1,000 neobladders: the 90-day complication rate". *Journal of Urology* 184.3 (2010): 990-994.

17. Hautmann RE., *et al*. "ICUD-EAU International Consultation on Bladder Cancer 2012: Urinary diversion". *European Urology* 63.1 (2013): 67-80.

18. Herr HW and Donat SM. "A re-staging transurethral resection predicts early progression of superficial bladder cancer". *BJU International* 97.6 (2006): 1194-1198.

19. Kamat AM., *et al.* "Expert consensus document: consensus statement on best practice management regarding the use of intravesical immunotherapy with BCG for bladder cancer". *Nature Reviews Urology* 12.4 (2015): 223-235.

20. Sylvester RJ., *et al.* "Long term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guerin, and Bacillus Calmette Guerin plus isoniazid in patients with intermediate and high risk stage Ta T1 urothelial carcinoma of the bladder". *European Urology* 57.5 (2010): 766-773.

21. Fernandez-Gomez J., *et al*. "Prognostic Factors in patients with nonmuscle-invasive bladder cancer treated with bacillus Calmette-Geurin: multivariate analysis of data from four randomized CUETO trials". *European Urology* 53.5 (2008): 992-1001.

22. Palou J., *et al.* "Female gender and carcinoma in situ in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette-Guerin". *European Urology* 62.1 (2012): 118-125.

23. Parker WP., *et al*. "Utilization and outcomes of radical cystectomy for high-grade nonmuscle-invasive bladder cancer in elderly patients". *Clinical Genitourinary Cancer* 16.1 (2018): e79-e97.

24. Metcalfe MJ., *et al.* "Impact of high-risk features and effect of neoadjuvant chemotherapy in urothelial cancer patients with invasion into the lamina propria on transurethral resection in the absence of deep muscle invasion". *European Urology Focus* 3.6 (2017): 577-583.

25. Oddens JR., *et al.* "The effect of age on the efficacy of maintenance bacillus Calmette-Guerin relative to the maitnence epirubicin in patients with stage Ta T1 urothelial bladder cancer: results from EORTC genitourinary group study 30911". *European Urology* 66.4 (2014): 694-701.

26. Mannas M., *et al*. "A risk-stratified approach to the management of high-grade T1 bladder cancer". *Current Opinion in Urology* 28.6 (2018): 563-569.

27. Giacalone NJ., *et al*. "Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience". *European Urology* 71.6 (2017): 952-960.

28. Raby SEM and Choudhury A. "Radiotherapy for High-Grade T1 Bladder Cancer". *European Urology Focus* 543 (2018): 1-3.

29. Vashistha V., *et al*. "Radical Cystectomy Compared to Combined Modality Treatment for Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-Analysis". *International Journal of Radiation Oncology, Biology, Physics* 97.5 (2017): 1002-1020.

30. Golombos DM., *et al.* "Robot-assisted partial cystectomy perioperative outcomes and early oncological efficacy". *BJU International* 119.1 (2017): 128-134.

31. Gontero P., *et al.* "Prognostic factors and risk groups in T1G3 nonmuscle-invasive bladder cancer patients initially treated with Bacillus Calmette-Guerin: results of a retrospective multicenter study of 2451 patients". *European Urology* 67.1 (2015): 74-82.

32. Kitamura H and Kakehi Y. "Treatment and management of highgrade T1 bladder cancer: what should we do after second TUR?" *Japanese Journal of Clinical Oncology* 45.4 (2015): 315-322.

33. Palou J., *et al*. "Recurrence, progression, and cancer specific mortality according to stage at re-TUR in T1G3 bladder cancer patients treated with BCG: not as bad as previously thought". *World Journal of Urology* 36.10 (2018): 1621-1627.

34. Audenet F., *et al.* "Is restaging transurethral resection necessary in patients with nonmuscle invasive bladder cancer and limited to lamina propria invasion?" *Urologic Oncology* 35.10 (2017): 603.e1-603.e5.

35. Yun S., *et al*. "How do we manage high-grade T1 bladder cancer? Conservative or aggressive therapy?" *Investigative and Clinical Urology* 57.1 (2016): S44-S51.

36. Gupta A., *et al.* "Outcomes of patients with clinical T1 grade 3 urothelial cell bladder carcinoma treated with radical cystectomy". *Urology* 71.2 (2008): 302-307.

37. Williams SB and Kamat AM. "Optimum management of non-muscle-invasive micropapillary variant urothelial carcinoma: possibility for missed chance of cure?" *BJU International* 118.3 (2016): 349-350.

38. Branchereau J., *et al*. "Prognostic value of the lymphovascular invasion in high-grade stage pT1 bladder cancer". *Clinical Genitourinary Cancer* 11.2 (2013): 182-188.

39. Ukai R., *et al*. "Lymphovascular invasion predicts poor prognosis in high-grade pT1 bladder cancer patients who underwent transurethral resection in one piece". *Japanese Journal of Clinical Oncology* 47.5 (2017): 447-452.

40. Fransen van de Putte EE., *et al.* "Metric substage according to micro and extensive lamina propria invasion improves prognostics in T1 bladder cancer". *Urologic Oncology* 36.8 (2018): 361.e7-361.e13.

41. Minardi D., *et al*. "Nonmuscle invasive high grade urothelial carcinoma of the bladder. Which factors can influence understaging at the time of radical cystectomy?" *Archivio Italiano di Urologia e Andrologia* 88.1 (2016): 13-16.

Volume 2 Issue 10 December 2018