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UROTHELIAL CANCER (S DANESHMAND, SECTION EDITOR)

High-grade T1 Urothelial Carcinoma: Where Do We Stand?

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Abstract

Purpose of Review Bladder cancer is a deadly and common malignancy, with 24% of new cases presenting as T1 disease. High-grade T1 in particular represents a difficult entity to treat due to its clinical variability and known risks of recurrence, progression, and cancer-specific mortality. The differences in guidelines from major urologic organizations underscore this variability, and the past year has seen another BCG shortage, further complicating management. Advances have been made in the molecular and genomic characterization of high-grade T1, and new clinical trials are available to investigate alternative therapies. In this review, we summarize the variations in guidelines, alternatives to BCG, emerging molecular and genomic discoveries, and recent clinical trials.

Recent Findings Adherence to guidelines for non-muscle-invasive bladder cancer in the community among practicing urologists remains low, in part due to the variations in available guidelines. In the era of a BCG shortage, decreased dosing schedules and alternative intravesical options are increasingly being used. New biomarkers are being discovered to better risk-stratify patients, with future therapies aimed at targeting aggressive disease.

Summary HGT1 urothelial carcinoma remains a highly variable and aggressive disease, but we are making significant progress in better characterizing the clinical and molecular factors that influence recurrence and progression, to better guide management.

Keywords High-grade T1 · Bladder cancer · BCG

Introduction

Bladder cancer remains a common and deadly disease with an estimated 80,470 new cases of and 17,670 deaths due to bladder cancer in the USA in 2019 [1]. Approximately 79% of new cases present as non-muscle-invasive bladder cancer (NMIBC), and 24% are specifically T1 disease [2]. The management of high-grade T1 (HGT1) urothelial carcinoma is particularly important given its clinical variability and known risks of recurrence, upstaging to muscle-invasive disease, and cancer-specific mortality. Appropriate management of HGT1 begins with thorough resection, re-resection in 3–6 weeks, and appropriate risk stratification. Intravesical therapy with Bacillus Calmette-Guerin (BCG) then follows as the standard of care [3]. However, there are variations in guidelines across different societies, highlighting the heterogeneity of the disease and its options for management. Moreover, we are again in an era of a BCG shortage necessitating alternative therapies and facing HGT1 that is refractory to standard BCG as well. In order to better understand this complex disease entity, there have been continued advances in the molecular and genomic profiling of HGT1 and several clinical trials to investigate immunotherapy options. In this review, we discuss the variations in HGT1 guidelines, alternatives to BCG in the BCG shortage era, emerging molecular and genomic discoveries, and recent clinic trials.

Variations in Guidelines

There are a number of guidelines available for NMIBC from various groups, including the American Urological Association (AUA), European Association of Urology (EAU), Canadian Urological Association (CUA), National Comprehensive Cancer Network (NCCN), Society of Urologic Oncology (SUO), National Institute for Health and Care Excellence (NICE), International Consultation on Urologic Diseases (ICUD), International Bladder Cancer

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Network (IBCN), International Bladder Cancer Group, and European Society for Medical Oncology (ESMO). The AUA/SUO have released joint guidelines, which are among the most commonly used, along with the EAU and NCCN guidelines [4].

The AUA/SUO, EAU, and NCCN guidelines were last updated in 2016, 2017, and 2019, respectively. All of these guidelines recommend complete resection of visible tumor if possible, with the EAU and NCCN guidelines specifically requiring muscle in the specimen to qualify as complete resection. The AUA/SUO guidelines do recommend a repeat resection with muscle in cases of T1 disease. A repeat resection is recommended by all guidelines for all T1 tumors to increase recurrence-free survival, improve BCG outcomes, and accurately stage the patient.

These guidelines all use the 2009 American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) TNM staging system, which was revised in 2017, except bladder tumors were unchanged. In terms of grading, the World Health Organization (WHO) 1973 system employs grades 1 to 3, while the WHO/International Society of Urological Pathology (ISUP) 2004 system changed to a low- and high-grade classification. The AUA and NCCN guidelines employ the WHO/ISUP 2004 classification, but the EAU guidelines allow for the usage of both. Several risk calculators, such as the European Organization for Research and Treatment of Cancer (EORTC) and the Club Urologico Espanol De Tratamiento Oncologico (CUETO) systems, use the WHO 1973 classification. While the updated classification is simpler to use, a recent study by van de Putte et al. found that Grade 3 lesions in the WHO 1973 system were negatively associated with progression-free survival and cancer-specific survival, but the WHO/ISUP 2004 system was not prognostic, after re-reviewing 601 slides of primary T1 bladder cancer [5].

In regard to immediate intravesical therapy following TURBT, the AUA/SUO and EAU guidelines both discuss a single dose of postoperative intravesical chemotherapy, in the absence of perforation, for suspected or known low or intermediate risk disease, based on their respective risk stratification tables. The AUA/SUO guidelines state that mitomycin C or epirubicin can be considered, while the EAU guidelines actually recommend a single dose of intravesical chemotherapy but do not specify a preferred agent. The EAU guidelines base the recommendation on several large meta-analyses that have demonstrated reduced recurrence rates compared with TURBT alone. However, they do clarify that mitomycin C, epirubicin, and pirarubicin have all been beneficial with no randomized comparisons to suggest greater efficacy of one medication over another. HGT1 disease is classified as high-risk in both groups' risk stratification, and so the benefit of immediate postoperative intravesical chemotherapy is unclear, although the diagnosis would not be made until pathology results return in the cases of initial resection. The NCCN guidelines differ in that single-dose intravesical chemotherapy, with a preference for gemcitabine, is recommended after all initial TURBT cases in the absence of perforation, due to a 35% recurrence rate reduction. They do clarify that it is not effective in patients with an elevated EORTC recurrence risk score.

Once the diagnosis of HGT1 disease is made, then the EAU guidelines recommend intravesical BCG for 1–3 years, unless there is concomitant carcinoma in situ (CIS), multiple tumors, tumors > 3 cm, variant histology, or lymphovascular invasion, in which case cystectomy should be discussed as an immediate option. The optimal duration of maintenance therapy has not been decided, but in an EORTC randomized control trial where 3 years were administered compared with 1 year, there was a reduction in recurrence rate of high but not intermediate risk disease. The AUA/SUO guidelines concur that a newly diagnosed HGT1 patient should receive a 6-week induction course of BCG followed by 3 years maintenance if they respond to the initial course. However, if the original TURBT reveals CIS, variant histology, or lymphovascular invasion, then immediate cystectomy should be considered. The NCCN guidelines strongly recommend a repeat TURBT after the initial diagnosis of HGT1 has been made, but immediate cystectomy can also be considered. If there is residual disease, then BCG or cystectomy follows. If there is no residual disease, then BCG, intravesical chemotherapy, or observation in select cases can be considered. BCG is preferred in these cases, and observation is only an option in the setting of a small volume tumor with limited lamina propria invasion and no CIS. No specific maintenance schedules have been studied, but the NCCN guidelines offer the Southwest Oncology Group schedule of 3 weekly instillations at months 3, 6, 12, 18, 24, 30, and 36 after a 6-week induction course.

In the cases of disease that is unresponsive to, recurs after, or progresses through BCG, there is significant discrepancy in management options. These cases can be categorized as BCG refractory, resistant, or relapsing. However, the guidelines do not specifically use these categorizations in all cases. The EAU guidelines classify BCG failure as progression to muscle-invasive disease during follow-up, BCG refractory tumor, or high-grade recurrence after maintenance BCG despite initial response to induction BCG. They define BCG refractory as high-grade non-muscle-invasive tumor at 3 months, or CIS at both 3 and 6 months, or if a high-grade tumor appears during BCG therapy. For BCG failure, cystectomy is the preferred option from the EAU guidelines. Alternative options include intravesical immunotherapy or chemotherapy, but they are considered to be oncologically inferior. The AUA guidelines do not use the above terms but recommend cystectomy in patients who are fit for surgery and have HGT1 after a single induction course of BCG given the significant rates of progression in this subset of patients. For

those who are unfit or unwilling to undergo cystectomy after two courses of BCG, then clinical trial enrollment is recommended, or intravesical chemotherapy if trials are not available. However, a second course of induction BCG is not specifically recommended in any HGT1 scenario. While not included in the guidelines, sequential gemcitabine and docetaxel has demonstrated promising results [6]. The NCCN guidelines also do not use the categorizations of BCG refractory or resistant disease, but instead offer a pathway that broadly includes recurrent or persistent cancer after induction BCG. If visible tumor is identified, then the recommendation is TURBT and a single dose of gemcitabine, followed by either adjuvant intravesical therapy or cystectomy. In the case of recurrent T1 disease in patients unfit for cystectomy, then chemoradiotherapy can be considered. If there is no visible tumor but positive cytology, and bladder biopsies are then positive, then BCG is recommended. Complete responders can continue with maintenance BCG, while incomplete responders can undergo cystectomy or another intravesical agent. In indeterminate cases on cystoscopy, the recommendation is TURBT and a single dose of gemcitabine, and if the pathology remains HGT1, then cystectomy is preferred [7–9]. The guidelines for HGT1 are summarized in Table 1.

These different guidelines and pathways underscore the significant variability and changing landscape of HGT1, which complicates its management. Thus, adherence to guidelines by urologists in the community remains low [4]. To make matters worse, we have now entered another BCG shortage era, as Merck, the only supplier of BCG to the USA, recently announced supply constraints due to increasing global demand.

BCG Shortage

Several BCG substrains have been developed, with the Connaught and TICE strains available in the USA. The Tokyo 172, Moreau, and Danish substrains are available elsewhere in the world. A prior BCG shortage was experienced after a Sanofi Pasteur (producer of Connaught strain) factory was flooded in 2011. In 2016, Sanofi Pasteur discontinued all of its BCG production in the USA. Thus, efforts have been made to explore the efficacy of other substrains and even other intravesical therapies to alleviate the detrimental effects of the shortage. A prospective randomized control trial demonstrated increased recurrence-free survival with Connaught over TICE, while another prospective study did not find a significant difference in response rate between Tokyo 172 and Connaught. An EORTC meta-analysis did not demonstrate a significant response difference between any of the strains [10]. An ongoing SWOG study (S1602) is comparing TICE with Tokyo 172.

Aside from the various strain options, the dosing and schedule of BCG administration also remains up for debate. A CUETO prospective randomized control study found that 1/3 dosing of BCG did not have worse rates of recurrence or progression compared with full dosing, specifically in HGT1 [11]. Carneiro et al. reviewed the usage of ½ dosing of Moreau BCG with full dosing in HGT1 and found no difference in recurrence, progression, or disease-specific mortality [12]. Furthermore, an EORTC randomized control trial demonstrated a lower recurrence rate, but no difference in progression or survival, with 1 year of maintenance BCG instead of 3 years, for high-risk patients, which includes HGT1. An EAU randomized clinical trial (NTR 4011) is ongoing to determine the optimal BCG schedule, as it is unclear if a 6-week induction course is necessary, or if it could be reduced to 3 administrations. Similarly, 2 administrations during maintenance therapy are being explored in lieu of 3.

Recent advances have also been made to improve the efficacy of intravesical BCG by first priming the immune system with subcutaneous BCG. This phenomenon has been demonstrated in an animal model, with T cells infiltrating the bladder without repeated intravesical instillations of BCG due to prior parental administration of BCG. In humans, BCG responses have been found to be greater in patients who have previously received BCG vaccines [13]. The ongoing SWOG study (S1602) is further exploring this process.

An alternative to BCG for intravesical therapy can be mitomycin C, which has demonstrated similar rates of progression and disease-specific survival when compared with BCG for NMIBC as a whole [14]. However, this data did not stratify by risk categories and may not be as applicable to the HGT1 population. Furthermore, chemohyperthermia has demonstrated promising results in several studies to improve the efficacy of intravesical chemotherapy. A systematic review by Lammers et al. reported a 59% reduction in recurrence with chemohyperthermia and mitomycin C compared with mitomycin C alone [15]. A randomized control trial comparing chemohyperthermia with mitomycin C and standard BCG in intermediate and high-risk NMIBC patients demonstrated a higher recurrence-free survival rate in the chemohyperthermia arm [16]. Again, these studies did not run a subanalysis of the HGT1 population, which does limit their applicability. Gemcitabine has become a chemotherapeutic option of interest and may be more effective than mitomycin C with less side effects. When compared with BCG, it has been found to be less effective in high-risk patients but more effective in BCG refractory patients [17]. The combination of gemcitabine and docetaxel has also been investigated with a reported recurrence-free rate at 1 year of 54% after a single induction course [18]. Other agents, such as doxorubicin and epirubicin, have been found to reduce recurrence compared with TURBT alone in a large systematic review, but were not found to reduce progression. The same systematic review did not find any beneficial effect of thiotepa [19]. Several immunotherapeutic treatments are under investigation as well, which will

Table 1 Guideline variations for HGT1

Guideline	Updated	Staging system	Pathology system	Risk groups	Post-TURBT intravesical therapy	Recommended intravesical chemotherapy	Initial HGT1 management	Immediate cystectomy for HGT1	Persistent HGT1 after induction BCG
AUA/SUO	2016	AJCC/UICC TNM	WHO/ISUP 2004	AUA Risk Stratification Table	Consider in suspected/known low/intermediate risk disease	Mitomycin C or epirubicin	Intravesical BCG for 6 weeks, then 3 years maintenance if responded to induction, unless CIS, variant histology, and/or lymphovascular invasion	If residual disease after repeat TURBT, CIS, variant histology, and/or lymphovascular invasion	Cystectomy
EAU	2017	AJCC/UICC TNM	WHO/ISUP 1973 or 2004	EAU Risk Group Stratification Table	Recommend in suspected/known low/intermediate risk disease	Unspecified	Intravesical BCG for 1–3 years, unless multiple tumors, tumors > 3 cm, CIS, variant histology, and/or lymphovascular invasion	Multiple tumors, tumors > 3 cm, CIS, variant histology, and/or lymphovascular invasion	Cystectomy
NCCN	2019	AJCC/UICC TNM	WHO/ISUP 2004	AUA Risk Stratification Table	Recommended for all cases	Gemcitabine	Repeat TURBT, then intravesical BCG, intravesical chemotherapy, observation, or cystectomy	After initial diagnosis or if residual disease after repeat TURBT	Adjuvant intravesical therapy or cystectomy

be discussed in the "Trials for High-grade T1" section of this article.

Upfront radical cystectomy remains a viable option for patients with HGT1, as delayed cystectomy is associated with worse survival rates in multiple series [20–22]. Lymph nodes are found to be positive in 9–18% of patients who have even undergone immediate or early cystectomy for HGT1 [23]. Moreover, in an international cohort of 1136 patients who underwent cystectomy for HGT1, 33.4% had non-organ confined disease at cystectomy, and 35.5% died of metastatic disease over a median follow-up of 4 years [24]. As it is well-known that 25–47% of patients with T1 disease will be upstaged at the time of cystectomy, several studies have investigated the prognostic indicators of muscle invasion [25]. This is especially important, since patients with HGT1 disease, who are upstaged at cystectomy, have worse cancer-specific survival [26]. Martin-Doyle et al. found depth of lamina propria invasion to be the most significant negative prognosticator in a large meta-analysis of 15,215 patients, and D'Andrea et al. recently developed a nomogram demonstrating lymphovascular invasion and variant histology to be critical to progression outcomes as well [27, 28]. A multi-center review of 2451 patients with HGT1 reported a progression rate of 19% with the most important prognostic factors being age > 70 years, size > 3 cm, and the presence of CIS [29]. Thus, patients with these factors should be considered more strongly for upfront cystectomy.

Biomarkers

As it is clear that HGT1 is a highly variable disease, there has been progress made to better characterize the malignancy at molecular and genomic levels. Predictors of muscle invasion, response to therapy, and survival outcomes are of particular interest to help guide management. Gaya et al. examined total p63, p53, and ΔNp63 expression in 134 HGT1 patients with a median follow-up of 62 months. They found that ΔNp63-positive patients were at low risk for disease progression and had better cancer-specific survival. Total p63 and p53 expression did not have any correlation with recurrence or progression [30]. However, a recent meta-analysis by Du et al. reported that overexpression of p53 was associated with an increased progression rate in T1 disease. Subgroup analyses demonstrated increased progression rates with HGT1 tumors and also HGT1 tumors after BCG [31].

In another study, the biomarkers galectin-3, CD44, E-cadherin (E-CAD), CD138, p16, survivin, HYAL-1, and topoisomerase-Iiα were evaluated in 92 HGT1 specimens that included single tumors < 3 cm in size with detrusor muscle present. In a multivariate analysis, topoisomerase-Iiα was a predictor of progression-free survival, while survivin and E-CAD were predictors of overall survival. Galectin-3, CD44, CD138, and HYAL-1 were not associated with survival outcomes [32]. An 8-gene progression-related classifier (coagulation factor C homolog, EGF LAG 7-pass G-type receptor 3, heme oxygenase 1, kinesin family member 1A, chromosome 16 open reading frame 74, methylthioadenosine phosphorylase, 6-phosphofructo-2 kinase/fructose-2,6-biphosphatase 4, and S100 calcium binding protein A8) was previously found to be predictive of outcomes in NMIBC. Kang et al. evaluated the role of this 8-gene signature in HGT1 and found that it was an independent predictor of muscle invasion in a multivariate analysis [33].

The role of human epidermal growth factor receptor-2 (HER-2) in bladder cancer has been controversial, potentially due to its evaluation in heterogeneous populations. In an analysis of HER-2 in the setting of HGT1 with and without BCG therapy, HER-2 overexpression was found to be a predictor of overall survival. It was also found to be a predictor of disease-free survival in both patients who had received BCG therapy and patients who had not. The same study also evaluated the microsatellite instability factors MutL homologue 1 (MLH1) and MutS homologue 2 (MSH2) in HGT1 and found that MLH1 was predictive of progression-free survival in patients treated with BCG, while MSH2 had no prognostic capability [34].

Specifically in HGT1 after BCG, heat shock protein 60 was positively associated with a greater progression rate, while heat shock protein 70 was negatively associated with progression and recurrence. Heat shock protein 90 demonstrated no relationship to progression or recurrence [35]. Twist2 is a transcription factor that is a regulator in epithelial-mesenchymal transition (EMT). EMT decreases cellular adhesion, which allows for increased cancer cell migration and metastasis in bladder cancer. High Twist2 expression in HGT1 tissue samples is associated with BCG unresponsiveness and progression to muscle-invasive disease [36].

Trials for High-grade T1

Immunotherapies have demonstrated promising results in muscle-invasive bladder cancer and other malignancies, and so they are now being explored for HGT1 and BCG-nonresponsive NMIBC in several clinical trials. The program death-ligand 1 (PD-L1) is an immune checkpoint that binds to program death protein-1 (PD-1) on T cells to suppress their function. Tumor cells have overexpressed PD-L1, which then creates a "molecular shield" [37]. Pembrolizumab, an antibody that targets PD-1, is being investigated as a single agent initial therapy for HGT1 after TURBT in a Memorial Sloan Kettering trial (NCT03504163), as well as in a Merck trial (NCT02625961) for patients with high-risk NMIBC unresponsive to BCG and ineligible or refusing radical cystectomy. Atezolizumab, a humanized monoclonal antibody that targets PD-L1, is being used in a National Cancer Institute trial (NCT02844816) in patients with recurrent BCG

Table 2 Current clinical trials

Trial name	ClinicalTrials.gov identifier	Sponsor	Status	Intervention	Study population
Phase II Study of Pembrolizumab (MK-3475) as First-Line Therapy for High Risk T1 Non-Muscle-Invasive Bladder Cancer	NCT03504163	Memorial Sloan Kettering Cancer Center	Recruiting	Pembrolizumab	BCG-naïve high-risk T1
A Phase II Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Subjects With High Risk Non-muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG) Therapy	NCT02625961	Merck	Recruiting	Pembrolizumab	BCG-unresponsive high-risk NMIBC
Phase II Trial of Atezolizumab in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer	NCT02844816	National Cancer Institute	Active, not recruiting	Atezolizumab	BCG-unresponsive high-risk NMIBC
An Open Label, Randomized, Phase III Trial, Evaluating Efficacy of Atezolizumab in Addition to One Year BCG (Bacillus CaLmette-Guerin) Bladder Instillation in BCG-naive Patients With High-risk Non-muscle Invasive Bladder cANcer (ALBAN)	NCT03799835	UNICANCER	Recruiting	Atezolizumab	BCG-naïve high-risk NMIBC
Intravesical Administration of Durvalumab (MEDI4736) to Patients With High-risk, Non-muscle-invasive Bladder Cancer (NMIBC). A Phase II Study With Correlative	NCT03759496	Hellenic GenitoUrinary Cancer Group	Recruiting	Durvalumab	BCG-unresponsive high-risk NMIBC
A Phase I Single-Arm Study of the Combination of Durvalumab (MEDI4736) and Vicinium (Oportuzumab Monatox, VB4-845) in Subjects With High-Grade Non-Muscle-Invasive Bladder Cancer Previously Treated With BCG	NCT03258593	National Cancer Institute	Recruiting	Durvalumab and vicinium	BCG-unresponsive high-risk NMIBC
An Open Label, Single Arm, Phase II, Multicenter Study of the Safety and Efficacy of CG0070 Oncolytic Vector Regimen in Patients With Non-Muscle Invasive Bladder Carcinoma Who Have Failed BCG Therapy and Refused Cystectomy	NCT02365818	Cold Genesys, Inc.	Completed	CG0070	BCG-unresponsive high-risk NMIBC
A Randomized, Prospective, Phase II Study to Determine the Efficacy of Bacillus Calmette-Guerin (BCG) Given in Combination With PANVAC[TM] Versus BCG Given Alone in Adults With High Grade Non-Muscle Invasive Bladder Cancer (NMIBC) Who Failed at Least 1 Induction Course of BCG	NCT02015104	National Cancer Institute	Active, not recruiting	PANVAC	BCG-unresponsive high-risk NMIBC
A Combined Phase 1 and Phase 2 Study of Albumin-bound Rapamycin Nanoparticles (Nab-rapamycin, ABI-009) in the Treatment of BCG Refractory or Recurrent Nonmuscle Invasive Transitional Cell Bladder Cancer	NCT02009332	Aadi, LLC	Recruiting	ABI-009	BCG-unresponsive NMIBC
A Phase II Protocol for Patients With Stage T1 Bladder Cancer to Evaluate Selective Bladder Preserving Treatment by Radiation Therapy Concurrent With Radiosensitizing Chemotherapy Following a Thorough Transurethral Surgical Re-Staging	NCT00981656	Radiation Therapy Oncology Group	Active, not recruiting	Radiation, cisplatin, fluorouracil, and mitomycin C	BCG-unresponsive high-risk NMIBC

unresponsive NMIBC with a primary endpoint of recurrence-free survival at 18 months. The ALBAN study from Unicancer (NCT03799835) is comparing atezolizumab with 1 year of BCG for high-risk NMIBC after TURBT to BCG therapy alone. Another similar immune checkpoint inhibitor, durvalumab, is being studied by the Hellenic Genitourinary Cancer Group (NCT03759496) to determine its effects on NMIBC after BCG. The National Cancer Institute (NCT03258593) is concurrently investigating durvalumab and vicinium in patients with high-grade NMIBC after BCG to determine safety and tolerability. Vicinium is an epithelial cell adhesion molecule-specific antibody fragment that inhibits protein synthesis in tumor cells after binding to epithelium cell adhesion molecule. CG0070, an oncolytic adenovirus, is being used by Cold Genesys Inc. in a trial (NCT02365818) for patients with high-grade NMIBC after

BCG, with a primary endpoint of durable complete response at 18 months. Another National Cancer Institute trial (NCT02015104) is comparing the TICE BCG alone and TICE BCG with PANVAC in patients with high-grade NMIBC who have failed at least 1 induction course of BCG. PANVAC is a recombinant virus vector vaccine with genes for carcinoembryonic antigen, mucin-1, B7.1, intracellular adhesion molecule-1, and leukocyte function-associated antigen-3. Albumin-bound rapamycin nanoparticles (ABI-009) are being studied by Aadi Bioscience (NCT02009332) in patients with BCG refractory disease to measure safety and tolerability. The Radiation Therapy Oncology Group (NCT00981656) is investigating the usage of chemoradiotherapy in stage 1 bladder cancer, with a primary endpoint of patients that are cystectomy-free at 3 years. A summary of current trials is provided in Table 2.

Conclusion

HGT1 urothelial carcinoma remains a highly variable and aggressive disease, but we are making significant progress in better characterizing the factors that influence recurrence and progression, to better guide management. The numerous guidelines and their variations are indicative of the gaps in our knowledge for the most efficacious treatment strategies. Advances in molecular and genomic profiling are helping us to better understand the different subtypes of the disease and tailor individualized therapies to them. Immunotherapies for NMIBC, and not just metastatic or muscle-invasive disease, represent an exciting new horizon.

Compliance with Ethical Standards

Conflict of Interest Wesley Yip and Akbar Ashrafi each declare no potential conflicts of interest. Siamak Daneshmand is a section editor for *Current Urology Reports*.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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