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REVIEW ARTICLE

OPTIMUM MANAGEMENT OF THE T_1 HIGH GRADE BLADDER CANCER

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Abstract

Objectives: *To determine the optimum treatment option for patients with superficial high grade (T_1Hg) bladder cancer.*

Introduction: *Controversy exists about the most appropriate treatment for superficial high grade (T_1Hg) bladder cancer. Immediate cystectomy offers the best chance for survival but associated with an impaired quality of life compared with conservative therapy. In case of conservative therapy lifelong surveillance is required and there is a high rate of recurrence and risk of disease progression. So optimum treatment option should be determined to treat the disease optimistically.*

Methods: *A comprehensive and systemic search of the pubmed database for English Language articles was performed using the following medical subject Heading (MeSH): Bladder cancer, treatment of superficial high grade (T_1Hg) bladder cancer, treatment options for bladder cancer, natural history of T_1Hg bladder cancer, newer Intravesical agents, cystectomy and in addition reference of relevant articles were searched for additional references.*

Results: *Approximately 70% of all newly diagnosed bladder tumors are non-muscle invasive bladder cancer. The management of these patients entails transurethral resection with or without adjuvant intravesical therapy. After review of obtained articles it is evident that the conservative treatment of T_1Hg bladder cancer should be ended when there is systemic or local toxicity from intravesical therapy or patient is not complaint or persistence of tumor or tumor progression despite therapy.*

Conclusion : *The management of T_1Hg is highly variable due to several factors including divergence in treatment related evidence. The efficacy of treatments must be balanced with their toxicity, so that single treatment option cannot be considered superior across all Non-Muscle Invasive Bladder Cancer (NMIBC). Immediate radical cystectomy may be offered upfront in patients with T_1Hg tumors with concomitant CIS or multiple recurrent high grade tumors.*

Key Words: *Bladder cancer, T_1Highgrade bladder cancer, treatment options for bladder cancer.*

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Introduction:

T_1Hingh Grade transitional cell carcinoma of the urinary bladder represents a highly malignant tumor with a variable and unpredictable biologic potential. Approximately 70% of all newly diagnosed bladder tumors are non-muscle invasive bladder cancers, including stage Ta, stage T_1 and carcinoma in situ (CIS)[1]. The management after these patients entails transurethral resection with or without adjuvant Intravesical therapy. Despite adequate therapy, however, 60-70% of these lesions will recur and 10-20% will progress to muscle – invasive disease, therapy requiring a radical cystectomy[2]. High grade superficial TCC of urinary bladder remains a difficult situation to manage even in premiere centers. Opinion defers as to whether

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conservative or radical surgery is appropriate when high grade (G_3) tumors are diagnosed. Monaharam et al[3] places the decision making in the management of T_1Hg tumors as the most difficult. In case of conservative therapy like intravesical maintenance BCG instillation, advantage is obvious, since the bladder is spared and therapy does not involve radical surgery with all its morbidity and morbidity. On the other hand, optimal chance of cure is possible in case of cystectomy but chance of overtreatment in a substantial percentage of patients[4]. There are good data supporting bladder conservative therapy with repeat transurethral resection and administration of bacilli Calmette Guerin (BCG) Intravesical therapy[5].

Patients who present with muscle invasive disease and distant metastases are usually managed by radical cystectomy or chemotherapy with or without radical cystectomy. But treatment decision for T_1Hg is not always straightforward. It presents a dilemma to the urologist whether to remove or not to remove the bladder?

Overview of T_1Hg bladder cancer

Bladder cancer is a common malignancy arising from urothelial cells and is responsible for considerable morbidity and mortality[6]. Approximately 70% of nearly diagnosed cases of bladder cancer are non-muscle invasive which is only confined to the urothelial and lamina propria of the bladder[7]. Among non-muscle invasive bladder cancer, around 70% present as Ta lesions (papillary growth invading the lamina propria), and 1% as carcinoma in situ[8]. T_1 tumors which are usually high grade have potential to become more aggressive, with higher rates of progression to muscle invasion and metastasis. Most subsequent studies also suggested that grade is a better prognostic factor to determine mortality than of recurrence [9-10]. Haney and colleagues have shown that the risk of disease progression to muscle invasion is strongly associated with tumor grade[10].

Natural History of T_1Hg Bladder Cancer

Up to one third of patients with NMIBC will progress to muscle invasive disease and have a higher risk of death from bladder cancer than those who do not progress[9]. A population based study of the natural history of the disease in the United States is done by Karim Chamie and colleagues. They analysed 7, 410 individuals with high grade non-muscle invasive disease who were diagnosed between 1992 and 2002. The research suggests that bladder cancer patients are at high risk for recurrence.

According to Christopher Saigal, the risk of recurrence has previously been linked with higher tumor grade and stage at diagnosis, the number of tumors at diagnosis, presence of CIS and continued smoking by the patient. Almost three fourth of the patients with high grade non-muscle invasive bladder cancer had a recurrence, progressed or died within a 10 years period. Approximately 41% of these patients will recur without progression, and an additional 33% will have progressive disease. Among those who progress, the researchers found, 4% will die of their bladder cancer.

The overall recurrence rate of non-muscle invasive bladder cancer is 60% to 70% and overall progression is 2% to 30%.[11-12]. Holmang and colleagues demonstrated that low-grade Ta tumors had a recurrence of 70% with a progression of only 2%. Patients with T_1Hg tumors have ten times the chance of muscle invasion and death than with other Ta – T_1 tumors with a risk of life long progression[13].

T_1Hg tumor progress in more than 50% of cases; deaths from disease occur in 25% of patients in the first 5years and in 10% of patients between 5 to 15 years[14].

Prognostic factors of recurrence and progression

Stage and grade

The two most important prognostic factor in non-muscle invasive bladder cancer are stage and grade. Bladder cancer is the fourth most common male cancer accounting for 7% of all cancers and the eighth highest cancer related mortality rate in American man[15]. Risk factors has been associated with bladder cancer include smoking, chronic inflammatory changes in the bladder (due to persistent bladder stones, recurrent urinary tract infections, indwelling catheters or schistosominsis), and chemotherapeutic exposure, such as cyclo-phosphamide[15-16].

Others factors

Six clinicopathological parameters such as grade, stage, tumor size, prior recurrence rate, presence of concomitant CIS and number of tumors are implicated with recurrence and progression. Tumor multiplicities has been shown to be an important factor in recurrence and progression in case of non-muscle invasive bladder cancer[17-18].

The lack of response to three months of Intravesical therapy has been found to be predictive of progression in T_1Hg disease[19].

Diagnosis:

Correct diagnosis is important for precise decision making. There is 48% of T1 tumors are under staged if muscle was not found in TUR specimen, and 14% of T1 were under staged if muscle was present in the specimen[20].

Biopsy:

To obtain specimen for histological assessment pure cutting current should be used during TURBT. There should always be muscularis propria in contact with the tumor in TURBT specimen. Some advocate cold cup biopsies of the tumor base and many urologists advocate a second TURBT in all patients with pT1 tumor after 10 days[17-20]. Manoharan et al recommend that a second TURBT be considered in patients with a T_1Hg tumor.

Pathology:

World health organization pathology guidelines recommended a conversion from previous classifications of grade G1, G2 or G3 to that of low or high grade papillary urothelial carcinoma[21]. Pathology reports should identify whether muscle tissue is present in the respected specimen or not.

Table-I

2004 WHO/ International society of urologic pathologists: Classification of non-muscle invasive urothelial neoplasia

Hyperplasia (flat and papillary)
Reactive atypia
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Non muscle invasive low grade papillary urothelial cancer
Urothelial carcinoma

Treatment options

In most cases of non-muscle invasive bladder cancer, tumors are treated initially with TURBT. A careful cystoscopic examination of the entire urethra and bladder surfaces precedes resection[22]. The position of tumors with reference to the bladder neck and ureteral orifices, the tumor configuration, whether tumors are papillary or sessile, and estimates of the number of tumor and their sizes should be noted to assist in future evaluation and follow-up. After resection of all visible tumors, adjuvant Intravesical immunotherapy or chemotherapy can be used.

Table-II

Current treatment options

Treatment	Indications
TURBT	Any suspected urothelial carcinoma; can be the sole treatment
Intravesical chemotherapy and immunotherapy	Non-muscle invasive urothelial carcinoma
Laser ablation therapy	Treatment of select lower and upper-tract cancer treatment of low grade
Conservative management	Papillary tumors
Fulguration or cystoscopic surveillance	Non-muscle invasive papillary bladder tumors Well-documented history of low-grade Ta tumors.

Why Dilemma in Selecting Treatment Option?

Following transurethral resection (TURBT) of the initial T_1Hg tumor without intravesical therapy there is a recurrence rate of 50-70% and progressions rate of 25% to 50%[23-24].

Radical cystectomy in high grade stage T1 transitional cell carcinoma offers excellent results in regard to the prevention of recurrence and progression and survival. The 5 years disease specific mortality after cystectomy for tumor not invading muscularis propria is 20% to 30%, but this mortality rate can be as high as 45% at 5 years and 70% at 10 years in case of conservative therapy[25-26].

So conservative management for those who develop recurrence may be considered as undertreatment. On the other hand radical cystectomy in case of minimal chance of recurrence should be considered as over treatments. Then what should be the optimum treatment option?

TURBT

Transurethral resection of bladder tumor (TURBT) is the first and gold standard treatment option for non-muscle invasive bladder cancer. The quality of the initial TRUBT specimen is of utmost importance. Transurethral resection of bladder tumor should include detrussor muscle in the specimen in an attempt to rule out T2

disease and minimize the risk of understanding. All visible tumors should be resected and resected specimen would provide histological type, grade and depth of invasion. In addition to potentially improving staging accuracy, repeat TURBT may also improve local control of disease[27].

Restaging

One study described that a pathology report of a repeat resection of T1 disease found the incidence of under staging was only 14% and there is also chance of overstaging in 25%-35% cases in the initial specimen. So the standard of care has progressed to mandatory restaging TURBT in case of T1Hg bladder cancer. Repeat resection may also provide prognostic information and improves the efficacy of Intravesical therapy[22].

Even when no residual disease is visible at repeat resection, the prior resection base should be biopsied. Herr has elegantly demonstrated that repeat TUR of non-muscle invasive disease 2 to 6 weeks after initial TUR can up-stage 29% of tumors and change disease management in up to 33%[20]. Therefore, a repeat TUR should be performed to decide the optimum option for management.

Intravesical immunotherapy

Intravesical therapy can be administered is an adjuvant fashion or as part of a maintenance regimen to prevent recurrence[28].

BCG

Bacillus Calmette-Guerin, a live attenuated strain of mycobacterium bovis, first indicated as a tuberculosis vaccine, has had widespread use in Intravesical immunotherapy sice the 1970s[29]. It has be come a first line treatment for carcinoma in situ and has been shown to be effective as prophylaxis to prevent bladder cancer recurrences following TURBT[30].

BCG is the only Intravesical agent that has been shown to affect tumor progression in several randomized trials [30-32]. Herr and colleagues evaluated 86 patients with high-risk superficial cancer and showed that the disease progression and mortality rates in patients treated with BCG decreased from 35% to 28% and 32% to 14% respectively[33]. Pansodoro and colleagues reported on 81 patietns with pT1G3 tumors who received an induction and maintenance regime, with median follow-up of 76 months and recurrence rate was 33%[34].

Table-III

Results of TUR plus BCG for T1G3 tumors.

Series/year	No. of patients	F/U (mo)	Recurrence (%)	Progre-ssion
Perake (2000)	44	43	27	16
Patard (2001)	50	65	52	22
Kulkarni (2002)	69	48	46	12
Bogdanovic	43	53	28	16
Peyromcure	57	53	42	23
Shahin	92	64	70	33

BCG Failure:

Although BCG is an effective adjuvant treatment for T1G3 bladder cancer approximately 50% of patients recur and 15% to 50% of patients within 5 year of BCG therapy[35]. BCG failure is defined as the presence of high-grade NMIBC at 6months from time of TURBT (or at 3 months if the initial tumor is T1G3) or only worsening of the disease (higher grade, stage or number of recurrences, or appearance of CIS) while on BCG therapy despite initial response to BCG [36]. Patients with high risk non-muscle invasive bladder cancer who fail BCG, the option of radical cystectomy should be recommended and discussed with the patient. Herr and colleagues compared the outcome of patients with NMIBC who received a radical cystectomy due to recurrence of disease within 2 years from initial BCG therapy with patients who received radical surgery after 2years; early radical cystectomy was associated with significantly improved survival[37].

Alternative treatments after

BCG failure

Interferon therapy

Patients with a diagnosis of less than stage T1 who do not respond favorably to BCG therapy may be candidates for salvage Intravesical therapy. A multicentre trail of patients with recurrence T1 and lack of response to BCG therapy and treated with reduced dose BCG plus interferon (50 milli units) reported a disease free rate of 42%at 24 months[38]. Intravesical interferon a-2B has been shown to have activity in non-muscle invasive urothelial carcinoma both as monotherapy and most recently in combination with low dose BCG therapy[39-40].

Newer Intravesical Agents

Gemcitabine

Gemcitabine is a newer promising Intravesical agent. In a phase-I study Dalbagni et al[41] reported that Intravesical gemcitabine was well tolerated with minimal bladder

irritation and acceptable myelosuppression. A complete response rate was achieved in 39% cases in a phase II study of patients with BCG refractory transitional cell carcinoma to determine the efficacy of gemcitabine as an Intravesical agent, 28 patients completed the therapy and 16 achieved complete response[42].

Paclitaxel

Paclitaxel is in the early stages of testing.

Cystectomy

Conservative treatment with TUR and Intravesical treatment is associated with continuous decline in survival with life long continuous decline in survival with life long risk of recurrence progression and metastasis[43]. The conservative treatment of T^1Hg bladder cancer should be ended when there is systemic or local toxicity from Intravesical therapy or the patient is not compliant or persistence of tumor or tumor progression despite therapy.

Timing of cystectomy

Early versus deferred: The timing of cystectomy is the most debated issue in the management of T_1Hg tumors. Several groups recommend immediate or early cystectomy without trial of adjuvant Intravesical therapy with or without repeat TUR. Because 5 year survival rate of 90% may decrease to 50% to 60% if radical cystectomy is delayed until progression[44]. In a series of 189 patients who underwent cystectomy within 3 months of diagnosis of muscle invasive disease there was a significantly better 5 year progression free survival than if cystectomy was performed more than 3months following diagnosis (55% and 34% respectively)[45]. Deferring cystectomy until progression to muscle invasive disease may decrease the overall disease specific survival[46]. T1Hg bladder cancer progresses to muscle invasive or metastatic disease at a rate of 30% to 50% after 5 years[47]. 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%[48-49].

Morbidity and mortality associated with cystectomy

Early complications can occur in upto 28% of patients and most can be managed without additional surgery[50]. Quality of life in bladder cancer patients after radical cystecomy and orthotopic bladder substitution is similar to quality of life of a normal matched population in terms of overall quality of life. Late morbidity is mainly due to the urinary diversion. The risk of impotence is high and age dependent[51]. The per-operative mortality with cystectomy is approximately 3%.

Conclusion

The management of T_1Hg is highly variable due to several factors including divergence in treatment related evidence. The high rates of recurrence and risk of disease progression in bladder cancer often require life long surveillance, making the disease both clinically and economically important. The efficacy of treatments must be balanced with their toxicity, so that single treatment option cannot be considered superior across all NMIBC. Immediate radical cystectomy may be offered upfront in patients with T_1Hg tumors with concomitant CIS or multiple recurrent high grade tumors.

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Abbreviations:

BCG	: Bacillus Calmette Guerin
T1Hg	: T_1Highgrade
TURBT	: Transurethral resection of bladder tumor
CIS	: Carcinoma in Situ
NMIBC	: Non muscle invasive bladder cancer.