

# Proactive approach to treat high-grade lamina-invasive bladder cancer

**Anil Mandhani**

Department of Urology and Renal Transplantation, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

## ABSTRACT

Urothelial cancer, despite advances in the field of medicine, remains an enigmatic problem with no tangible solution to treat it once it goes beyond the detrusor muscle. Nonmuscle-invasive bladder cancer form the majority of bladder cancer at presentation and high-grade lamina-invasive bladder cancer (HGLIbc) previously known as T1G3 is the most controversial subtype as far as treatment is concerned. Should the patient be given BCG or is an initial cystectomy a better outcome? If BCG is started should the patient be kept on maintenance? Urothelial cancer has no effective adjuvant treatment, therefore being proactive in identifying aggressive tumors to begin with would help in improving survival. This short review, based on the contemporary literature has tried to evolve an approach which may help in making clinical decision to treat HGLIbc.

**Key words:** Bacillus calmette guerin, high-grade lamina-invasive bladder cancer, radical cystectomy

## INTRODUCTION

Bladder cancer is the fourth most common cancer in men and 10<sup>th</sup> most common cancer in women in North America.<sup>[1]</sup> In India bladder cancer is the fifth most common cancer in men according to Delhi based registry with age adjusted incidence rate of 5.8/100,000 person years.<sup>[2]</sup> Incidence is much lower in females with 1.5 cases /100,000 person years.<sup>[2]</sup> In India the distribution of histopathological types has been reported as 97% TCC, whereas squamous cell carcinoma and adenocarcinoma accounts for 1.04% and 1.25% of the patients, respectively.<sup>[3]</sup>

In clinical practice about 70-75% of patients present with nonmuscle-invasive bladder cancer (NMIBC) and the rest 25-30% have muscle-invasive bladder

cancer.<sup>[4]</sup> Of these NMIBC tumors, about 70-75% are limited to urothelium and 25% invade the lamina propria.<sup>[4]</sup> About 20% of NMIBC are high-grade T1 (formerly T1G3).<sup>[5]</sup>

Bladder cancer is a disease of elderly but recently younger people are being detected with this disease. The median age at presentation is 60 years (range: 18-90 years). [Figure 1] The male to female ratio in the world literature is 4:1 but in Indians it is predominantly the disease of male population with a male to female ratio of 8.6:1.<sup>[3]</sup> [Figure 1]

## CHANGES IN TERMINOLOGY

“Superficial bladder cancer” to describe Ta and T1 has been used less frequently and has been replaced by a more appropriate term called NMIBC.<sup>[6]</sup> Unfortunately NMIBC also encompasses two different groups of tumors i.e. Ta and T1 requiring two different forms of treatment. Similarly previously known term as T1G3 is being classified as “high-grade lamina-invasive bladder cancer” (HGLIbc) according to WHO ISUP classification 2004.<sup>[7]</sup>

The treatment plan of HGLIbc can be perplexing. Should the patient be given BCG or is an initial cystectomy a better outcome? If BCG is started should the patient be kept on maintenance?

Urothelial cancer despite advances in the field of medicine remains an enigmatic problem with no tangible solution to treat it once it goes beyond the detrusor muscle. NMIBC presents to us a window of opportunity which

**For correspondence:** Dr. Anil Mandhani, Department of Urology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh – 226 014, India.  
E-mail: mandhani@sgpgi.ac.in

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should be managed carefully to achieve a cure from this disease. This short review based on contemporary evidence may help in taking decision to treat HGLIbc.

### IS MY INITIAL RESECTION COMPLETE?

Transurethral resection of the bladder tumor (TURBT) is the most underrated procedure and often left to the trainee residents. With the current techniques available, TURBT is an incomplete procedure. Therefore, the rate of residual tumor and under staging after initial TURBT has been reported between 28% and 74% and 1.7% and 64%, respectively, in different studies.<sup>[8-10]</sup> Thus, there is indication for relook TURBT if histopathology shows T1 high-grade lesion following resection of all visible tumor.

There is a role of intravesical Mitomycin C immediately after first TUR of the bladder tumor.<sup>[11-13]</sup> Relook TURBT is recommended within 2-6 weeks from the initial TURBT. In some guidelines it is also recommended to be done even if one obtains muscle in the first TURBT, which shows no

malignancy.<sup>[11-13]</sup> A recent randomized trial underscores the inadequacy of the current method to do TURBT as even after complete resection, which is defined as eradication of all macroscopic tumors, the underlying bladder wall with the detrusor muscle and the edges of the resection area, 33% had residual tumor and 7.6% were upstaged.<sup>[14]</sup> Therefore, as of now there is no single method to achieve a complete local control of HGLIbc.

### IS THERE ANY WAY TO ENSURE COMPLETE RESECTION?

Fluorescence cystoscopy may improve the detection rate of malignancy over the conventional cystoscopy thereby reducing the recurrence rate. Unfortunately due to low specificity of fluorescence cystoscopy, false-positive results may occur in patients with inflammatory lesions more so following the use of intravesical therapies. Therefore, it is not recommended as a routine procedure and currently the conventional white light cystoscopy remains the standard.<sup>[15,16]</sup>

### BCG OR RADICAL CYSTECTOMY FOR HIGH-GRADE LAMINA-INVASIVE BLADDER CANCER

Management of NMIBC is an ongoing process and one can not solely depend on initial plan according to the stage and grade. It is well known that survival is better with T1 disease than T2 and greater.<sup>[17,18]</sup> Does that mean that all HGLIbc should be offered radical cystectomy (RC)?

If a patient has tumor on first cystoscopy after the initial TUR and BCG (BCG refractory) and have an early recurrence

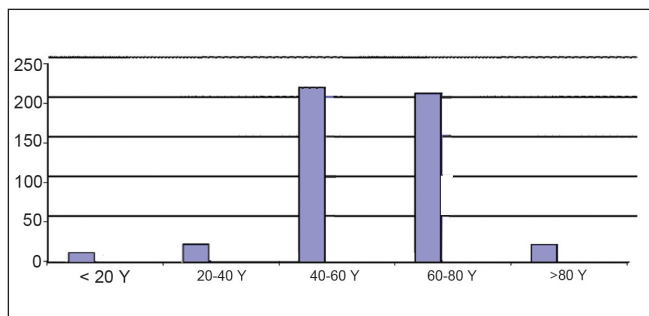


Figure 1: Age distribution of bladder cancer in Indians

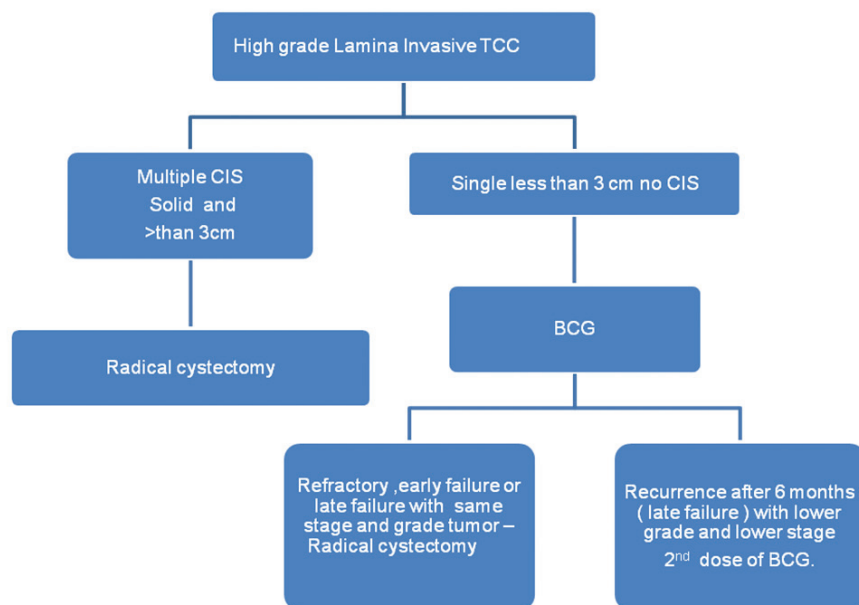


Figure 2: Proactive approach to high-grade lamina-invasive bladder cancer after relook transurethral resection of the bladder tumor

i.e., within 6 months (early BCG failures) they should be considered for early cystectomy.<sup>[19,20]</sup> [Figure 2] Similarly patients who initially have complete response to BCG treatment for 6 months and then have recurrence afterwards are termed as late BCG failures.<sup>[3]</sup> If recurrence is of a lower grade then a repeat induction course of BCG should be given and if recurrence is of the same grade and stage then cystectomy should be considered.<sup>[20,21]</sup> [Figure 2]

In one retrospective study comparing the contemporary cohort of early cystectomy with a historical cohort of delayed cystectomy i.e., waiting for muscle invasion to happen, after initial TUR and BCG at first recurrence of T1 stage, there was a significant difference in number of deaths due to disease and that is 48% with historical control and 31% with contemporary cohort.<sup>[18]</sup> In a similar study patients who opted for immediate cystectomy had significantly better 10-year disease-specific survival 78% vs. 51%.<sup>[22]</sup> These studies though not prospective but suggest the advantage of an aggressive treatment for high-risk patients.

No two patients of HGLIbc behave in the same way. Therefore, there should be something more than the pathological characteristics, i.e., stage and the grade, which could predict the outcome. Molecular differentiation characterizing the nature of TCC has been studied and research is going on to type and stage TCC based on molecular profiling of various genetic disorders to reclassify the tumor.<sup>[23,24]</sup> Till we have the means to pick HGLIbc for cystectomy, a clinical discretion based on the evidence should help in decision making.

### IS BCG BETTER THAN CYSTECTOMY FOR HGLIBC?

We know that TURBT is often an inadequate treatment for HGLIbc. After the initial histopathology, the urologist has to decide between early cystectomy and intravesical BCG immunotherapy.

'Carcinoma in situ' (CIS) is an ominous finding, adversely affecting the outcome in patients with HGLIbc. The risk of progression of T1G3 without CIS at 5 years is 29% but with the presence of CIS it increases to 74%.<sup>[25]</sup> CIS associated with T1 has predilection for lymph nodal involvement which has been reported in one series as 12%.<sup>[25]</sup> Similarly tumor of more than 3-cm-size doubles the risk of progression. European organization for research and treatment of cancer (EORTC) has defined risks factors for NMIBC for recurrence and progression. CIS, T1, high-grade, multiple Ta tumors, and >3cm are high-risk tumors and have probability of recurrence and progression at 5 year as 78% and 45%, respectively. An electronic calculator to categorize the patient in various risk groups and calculate the rate of recurrence and progression is available at <http://www.eortc.be/tools/bladdercalculator>.

With such a high risk of progression should we choose BCG for HGLIbc and lose the window of opportunity where disease could turn into a metastatic one where cure is not possible?<sup>[17]</sup> There is ample evidence that BCG prevents recurrence but BCG does not help in reducing progression. A meta-analysis by Sylvester *et al*<sup>[26]</sup>, demonstrated the benefit of adjuvant BCG on progression. Analysing 24 trials involving 4863 patients, 9.8% of patients receiving BCG progressed compared with 13.8% of controls thus only 4% of patients had actual risk reduction at a median follow-up of 2.5 years. In one retrospective study on the natural history of 86 patients with high risk, Ta, CIS and T1 lesions treated with TUR alone or with intravesical BCG, 34% of patients were dead from bladder cancer and only 27% were alive with functional bladder at 15 years. Thus the authors concluded that there was no advantage of BCG in the long term. This dismal outcome was despite the cohort containing 56% patients with high-grade Ta disease.<sup>[27]</sup>

Another relevant question to ask is; does reduction in recurrence mean improvement in survival? In one study, at median follow-up of 5.3 years, BCG did not appear to affect disease-specific survival.<sup>[28]</sup> Deferring cystectomy and starting BCG therapy initially in high risk NMIBC has also not resulted in better survival<sup>[29]</sup> In this study 90 patients with NMIBC (70 HGLIbc) who had cystectomy after BCG therapy of 1-3 courses for progression or recurrent tumor were analyzed. Fifty nine percent had cystectomy in less than a year and of these, 59% due to progression and rest due to recurrence. The disease specific survival did not differ for recurrence and progression of the disease. That means postponing cystectomy once there was progression or multiple recurrences, did not give survival advantage rather 19% died of disease and 11% had LN metastasis.<sup>[29]</sup> Once the high-risk NMIBC became MIBC, survival after RC was 50%. And if high-risk NMIBC was treated with RC to begin with the survival was 80%.<sup>[30]</sup>

### IS IT SO THAT GIVING MAINTENANCE BCG WOULD IMPROVE SURVIVAL IN THE LONG RUN?

Many individual analyses including randomized trials have shown the benefit of maintenance BCG, but there is no consensus on the dose and protocol of maintenance BCG. Should ambiguity in the treatment protocol in itself indicate an ineffectiveness of maintenance BCG is anybody's guess! With the most talked about SWOG protocol of maintenance BCG, only 16% could complete the full maintenance schedule.<sup>[31]</sup> In a critical analysis of all meta-analysis and randomized trial published on BCG induction and maintenance including its comparison to chemotherapy, rate of progression of disease with maintenance BCG has been shown to be equal to the one with induction therapy of six doses and that is 10%.<sup>[32]</sup> One thing which one must keep in mind while interpreting these trial is that most of them do not include subset analysis exclusively for high-

grade lamina-invasive TCC where we would expect even worse results.<sup>[23]</sup>

## IS THERE ANY DOWNSIDE OF CYSTECTOMY FOR HIGH-GRADE LAMINA-INVASIVE TUMOR?

RC with orthotopic neobladder (ONB) is an intricate procedure and there is a mortality rate of 1-3% and a morbidity rate of 25-45%.<sup>[33]</sup> Better surgical techniques and perioperative management have resulted in an improvement in both major and minor morbidity. There has been an association of higher surgical volume and reduced morbidity. This should form a basis for centralization for doing major surgery and encourage referral.<sup>[34]</sup>

ONB has its own drawbacks of Complications like metabolic acidosis, electrolyte disturbance, mucus retention requiring frequent wash, UTI and upper tract deterioration. Despite these, in a recent collaborative review from major centres doing ONB, it is regarded as the safe and preferred mode of diversion provided there are no contraindications. One can achieve a good long-term functional and oncological outcome if patients are treated in a high-volume institution by an experienced surgeon. It would always be useful for our patients if instead of doing repeated TUR for those who would likely to benefit from RC, one should refer such patients to centers performing RC and ONB.<sup>[35]</sup>

## CONCLUSIONS

Urothelial cancer has no effective adjuvant treatment; therefore, being proactive in identifying aggressive tumors would help in improving survival. NMIBC is a window of opportunity which should be managed carefully to achieve cure from this disease. Published guidelines based on various levels of evidence may help but in real life practice at times it becomes difficult to take a decision as every patient may not have the ideal indications described in guidelines. A vigilant urologist with a proactive approach as described in this review would help in taking decision to treat HGLIbc.

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