

Best Practice for the High risk Non Muscle Invasive Urinary Bladder Cancer

High grade superficial transitional cell carcinoma (TCC) of urinary bladder remains a difficult situation to manage even in premiere centers. Opinions differ as to whether conservative or radical surgery is appropriate when high grade (G3) tumors are diagnosed. Following transurethral resection (TURBT) of the initial T1G3 tumor with no additional therapy, there is a recurrence rate of 50% to 70% and a progression rate of 25% to 50%.

The risk of recurrence and progression in patients with T1G3 cancer increases with the duration of follow-up, may finally lead to death from cancer. Poorly differentiated (Grade3) tumors, named high grade urothelial carcinoma in the new World Health Organization (WHO) and International Society of Urological Pathology (ISUP) system have cells that do not differentiate as they progress, marked nuclear pleomorphism, high nuclear-cytoplasmic ratio and frequent mitotic figures constitute the histologic picture. T1G3 tumors, by definition invade the lamina propria without involving the muscularis propria. The problem with T1G3 tumors is that a systematic approach cannot be proposed for its treatment because of the very diverse potential for progression of these tumors.

The probability of progression to muscle-invasive cancer within 5 years of diagnosis is highest for this group of patients, and ranges from 25% to 50% and the progression is invariably associated with a decreased survival. Thus, accurate identification of grade and stage and a carefully thought out and managed treatment plan are paramount to achieving durable disease control and ensuring long-term survival.

Accurate staging is imperative for proper treatment planning, is particularly important in patients with high grade (G3) tumor. Consideration should be given to asking a referee pathologist to review the specimen, as there is significant variability in the accuracy of assigning clinical stage and grade. Up to 40% of patients who undergo radical cystectomy are under staged; this would lead to inappropriate therapy if a T2 tumor were misidentified as a T1 tumor. Therefore, re-resection of

the bed of a T1G3 tumor within 4–6 weeks of the initial transurethral resection of bladder tumor is essential for accurate staging.

Detrusor-muscle tissue should be included in the specimen to ensure accurate stage determination. Muscle bundles in the lamina propria, the muscularis mucosae, can be misinterpreted as muscle invasion.

If persistent T1G3 tumor is found, serious consideration should be given to radical cystectomy. The presence of lymphatic or vascular invasion, if confirmed by a referee genitourinary pathologist, should also prompt consideration of radical cystectomy. Other indications for radical cystectomy are micropapillary disease (a particularly aggressive variant of TCC), primary adenocarcinoma, and squamous cell carcinoma—none of which are considered responsive to intravesical therapy.

Understanding the status of the normal-appearing mucosa is important in identifying patients with associated carcinoma in situ (CIS). The combination of CIS with T1G3 cancer is associated with a higher risk of progression.

Hydronephrosis on the same side as the tumor is highly significant, in that it implies a muscle-invasive cancer. Upper-tract evaluation should be continued annually for the life of the patient, as there is a ≤ 20 –25% incidence of upper-tract tumors 10 years after diagnosis of high-risk disease.³

The treatment of choice for CIS and the prophylaxis of completely resected, high-risk papillary disease is a 6-week induction course of bacille Calmette–Guérin (BCG). Peak induction of cytokines occurs around the fourth treatment, and is sustained through to the sixth treatment⁴. Maintenance therapy consists of three weekly instillations administered at 3 and 6 months, then at 6-month intervals up to the 3-year mark.⁵

Although BCG is an effective adjuvant treatment for T1G3 bladder cancer, approximately 50% of patients recur and 15% to 50% of patients progress within the

first 5 years following BCG therapy. Interpreting the results from many of the studies is difficult because of differences in the definition of BCG failure. Herr and Dalbagni defined the 'BCG refractory state' as the failure to achieve a disease free state by 6 months after initial BCG therapy with either maintenance or retreatment at 3 months because of either persistence or recurrent disease. 'BCG relapse refers to recurrence after achieving disease-free status at 6 months. In this situation, the safest approach is to proceed with radical cystectomy, to avoid the risk of subsequent progression to muscle-invasive cancer, which is associated with a lower probability of survival.⁶

When this is not feasible, or when the patient recurs with low-risk or intermediate-risk disease (TaG1, TaG2, or multifocal papillary disease that is not high grade), an alternative approach is to use BCG in combination with interferon α . Two phase II studies and a large, three-arm, comparative trial led by O'Donnell clearly demonstrate that some patients can achieve a durable complete response with this regimen.⁷ The response rates to salvage combination immunotherapy of patients who have failed two prior BCG regimens or never achieved a complete response with BCG are low, and these patients should be advised to undergo cystectomy.⁸

It is important to realize that there are no data at this time from randomized, clinical trials to support the use of combination immunotherapy as the initial treatment for high-risk disease. Other salvage intravesical treatment options are being evaluated in clinical trials. Gemcitabine, an active agent for the treatment of metastatic TCC, has shown activity in several phase II trials of intravesical therapy, and will be evaluated in patients who have failed at least one course of BCG in a SWOG trial.^{8,9}

Mitomycin, combined with hyperthermia, has shown significant activity in intermediate-risk and high-risk patients, including those who have failed BCG.¹⁰ But by enlarge the mentioned therapies can only be recommended to only to them who are unwilling or absolutely unfit to undergo Nerve sparing Radical Cystectomy and urinary reconstruction.

Minimal mortality and morbidity with cystectomy

The perioperative mortality often cited with contemporary cystectomy series is approximately 3% and does not appear to be related to the choice of urinary

diversion performed. Early complications can occur in up to 28% of patients and most can be managed without additional surgery.¹¹

Quality of life in bladder cancer patients after radical cystectomy and orthotopic bladder substitution is similar to quality of life of a normal matched population in terms of overall quality of life. A study demonstrated no difference in the prevalence of depression, anxiety, subjective quality of life and low or moderate psychological well-being between the two groups.

Furthermore, quality of life appears to be equivalent among different types of urinary diversion. Potency is partially age-dependent but can be preserved in up to 20-62% of patients through nerve-sparing techniques. In male patients, using the nerve-preserving techniques learned from radical prostatectomy was proven to minimize the negative impact of surgery on sexuality and continence. In the same line, it was recently suggested to leave en-place the prostate capsule for ileal neobladder anastomosis.¹²⁻¹⁵

Staging transurethral resection of the prostate was first performed to confirm the absence of prostatic involvement by the tumour, in which case the capsule was left intact ensuring optimal reservation of the neurovascular bundles and of the innervation of the distal sphincter. The functional results were outstanding with up to 97% of patients reported to be completely continent day and night, and 82% of the patients who were sexually active preoperatively who retained their full potency.

If further confirmed, such technique would indeed compare well on a functional basis with the currently available conservative treatments. In all surgical series, the best results in terms of sexual function and continence were observed in young patients. Similar negative influence of age was reported after bladder replacement in terms of long-term reservoir capacity, nocturia and continence status.

As a whole, radical cystectomy techniques can be successfully adapted to the preservation of quality of life. It is recommend that radical surgery should be considered early in those young patients who are expected to benefit more from quality of life orientated techniques and who because of their longer life expectancy are more exposed than older patients to relapse and progression after conservative treatment.¹²⁻¹⁵

Our own cohort consisted of 221 patients with T1G3 from Jan 1995 to Dec. 2000 at Bangabandhu Sheikh Mujib Medical University and comfort Nursing home, Dhaka Bangladesh. In this historical cohort the 35 patients with documented T1 G3 were initially treated with Preemptive immediate Radical cystectomy. At 5 years the cumulative incidence of death from disease was 0% and 10 years survival was 95%. Operative mortality was 0% and the postoperative complications and morbidity was 14% and all of which were effectively treated.

On the other arm 60 patients under went bladder preservation technique with repeat TURBT, BCG installation therapy and in some cases BCG and Interferon installation. 90% of all patient eventually proven to be muscle invasive disease confirmed on Re TURBT at some stage of the observation period and underwent a radical cystectomy and 60% patient shown to be lymph node positive for malignancy. The 5 year survival was about 65% and 10 years survival become 45%.

Conclusions:

Preemptive radical cystectomy performed for recurrent T1 disease following intravesical bacillus Calmette-Guerin therapy may be associated with better disease specific survival¹⁶. Finally, radical cystectomy can be the first treatment of choice for patients with high-grade T1 disease, or for patients with multifocal CIS. Possible indications for cystectomy include multifocal disease, deep involvement of the lamina propria, and associated CIS. The 5-year disease-free survival rate with radical cystectomy is approximately 85% for patients with pathologic node-negative High grade T1 tumors, and 95% for pathologic stage pT0, pTa or pTis tumors, making radical cystectomy an excellent initial treatment for selected high-risk patients.¹⁶

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