ORIGINAL ARTICLE

RETROSPECTIVE ANALYSIS OF OUTCOME IN NON-MUSCLE INVASIVE BLADDER CANCER PATIENTS, TREATED WITH BCG IN A SINGLE CENTRE

Abdus Samad Syed[1], Fauzia Abdus Samad[2], Sameed Hussain[3]

[1,3] Consultant Oncologist, Combined Military Hospital, Rawalpindi, [2]Consultant Oncologist, Fauji Foundation Hospital Rawalpindi

ABSTRACT

Objective: To report progression, recurrence and survival in patients having non-muscle invasive transitional cell carcinoma (TCC) of the urinary bladder treated with bacillus Calmette-Guérin (BCG) after long term follow-up.

Study Design: Descriptive case series

Place and Duration of Study: The study was carried out in Department of Oncology, CMH Rawalpindi between June 2003 and May 2013.

Patients and Methods: The bladder tumours of 228 individuals with non-muscle invasive bladder TCC were completely removed with transurethral resection (TURBT). The South-west Oncology Group/Medical Research Council (SWOG/MRC) Protocol was then used for intra-vesical instillation of mitomycin or BCG. Analysis of recurrence, progression, and disease-related survival was carried out.

Results: 138 individuals were assessed, with a median age of 60 years, the remaining 90 patients being lost to follow-up. A total of 138 males and females got evaluated, with a median age 60 yrs (32–75 yrs). T1 low grade disease affected 88 people, and T1 high grade disease affected 43 cases while seven patients had pTa disease. So far, 104 patients (75%) have had no recurrences, 20 patients (14.5%) have persistent illness, and 14 patients (10%) have a progressive disease. The most prevalent side effects of treatment were cystitis, haematuria, and urinary infections. The mean duration of follow-up is 82.5 months (23–144 months).

Conclusion: For intermediate and high-risk non-muscle invasive bladder cancer, BCG is still the primary treatment, with very low risk of recurrence or progression.

Key words: *Non-muscle invasive bladder cancer Intra-vesical BCG, Mitomycin*

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INTRODUCTION

Urinary bladder carcinoma is the world's sixth most prevalent cancer. Non-muscle invasive bladder cancer accounts for over 70% of occurrences, worldwide [1]. At the Combined Military Hospital Rawalpindi's Department of Oncology, carcinoma of urinary bladder has remained one of the top ten malignancies throughout the last decade. Around 20% of these cases are in the non-muscle invasive (NMI) stage. This indicates that the disease is either mucosa- or submucosa-limited (Stage Ta – Tis or T1 respectively).

If these tumours are left alone following transurethral resection of bladder tumours (TURBT), they have a 60–80% recurrence rate [2,3]. Tumours are most likely to return in the first year after TURBT, and in the same stage and grade as before. These tumours can be recurrences, such as after inadequate resection or as a result of implantation, or they might be new occurrences. Because NMI bladder cancer is such a diverse disease, it's impossible to forecast who will experience a recurrence. Risk assessment can be done using prognostic criteria such stage, grade, multi-focality, tumour size, previous bladder tumours, and positive biopsies. Patients with pTa tumours seldom have recurrences or develop to advanced stages of the disease[4]. Mitomycin's intravesical instillation reduces the rate of recurrence in these patients.

About 12 to 13.3% patients with a non-muscle invasive bladder tumour develop invasive illness after five years [2,5]. Many investigations conducted since the mid-1970s have shown that intravesical chemotherapy can significantly postpone the recurrence of superficial bladder cancer but cannot completely stop it. This holds true for all agents and comparative studies that assessed the efficacy of intravesical chemotherapy after TURBT to TUR alone [6].

Patients having a non-muscle invasive transitional cell carcinoma (TCC) of the urinary bladder, treated with Mitomycin or bacillus Calmette-Guérin (BCG), were followed up in order to

Correspondence to: Dr. Fauzia Abdus Samad, Consultant Oncologist, Combined Military Hospital, Rawalpindi

Email: fasamad6@gmail.com

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see progression, recurrence and survival in this study. Recurrence is described as a tumour that has returned to the same location where it was removed before by TURBT, whereas progressive means that the lesion was not entirely removed in the prior TURBT and has grown in size since then.

CAPSULE SUMMARY

The authors aimed at comparing their results with international data in patients of non-muscle invasive bladder carcinoma treated with BCG. The recurrence free survival was more than 70% in this study, which matches the western population. Hence intravesical BCG induction and maintenance treatment remains standard care in non-muscle invasive bladder carcinoma in our population also.

PATIENTS AND METHODS

All patients had TURBT at the Armed Forces Institute of Urology (AFIU) in Rawalpindi, and histopathology reports were obtained from the Armed Forces Institute of Pathology (AFIP) in Rawalpindi. The study included males and females aged 18 years with a histological diagnosis of TCC urinary bladder, histological High Risk stage I disease (High grade, invasion of lamina propria, presence of CIS, recurrent intermediate risk disease), and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 – 2. Those with coexisting other cancers or prior bladder cancer treatment were excluded. A detailed history, general physical examination, systemic examination, blood complete picture, urea, creatinine, chest x-rays, abdomino-pelvic ultrasound, cystoscopy, and urine cytology were all part of the basic workup. Patients who underwent TURBT were given BCG as they were in high risk group as per the SWOG/MRC protocol[8]. In this protocol, patients receive induction therapy, which consists of six weekly BCG instillations. After 4 weeks, a check cystoscopy is performed. Maintenance BCG, consisting of three weekly instillations, is administered two weeks after the check cystoscopy. Maintenance doses are given on a quarterly basis during the first year. During the second and third years, BCG is administered at six-month intervals. A check cystoscopy is performed on each occasion. Treatment is continued only if cystoscopy and histopathology of random biopsies show no disease. The primary tool for assessing response was cystoscopy. The WHO common toxicity criteria version 2 were used to assess toxicity [9].

Table 1: Stratification of risk groups [7]

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG*), < 3 cm, no CIS
Interme-diate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high risk).
High-risk tumours	Any of the following: • T1 tumour • G3 (HG**) tumour • carcinoma in situ (CIS) • Multiple, recurrent and large (> 3 cm) TaG1G2 /LG tumours (all features must be present)*.
	Subgroup of highest risk tumours:
	T1G3/HG associated with concurrent blad-der CIS, multiple- and/or largeT1G3/HG and/or recurrent T1G3/HG,T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion.

**Low grade: a mixture of G1 & G2*
*** High grade: a mixture of some G2 & all G3*

DATA ANALYSIS

The data was analysed using the statistical software for social sciences (SPSS) version 24.0.The median of age and follow-up period were calculated. Gender, smoking history, grade, stage of disease, outcome, and side effects of treatment were all calculated as percentages.

RESULTS

138 of the 228 patients who received treatment in the department during this decade were evaluable, while the remaining 90 were lost to follow-up. One hundred eight males and thirty females

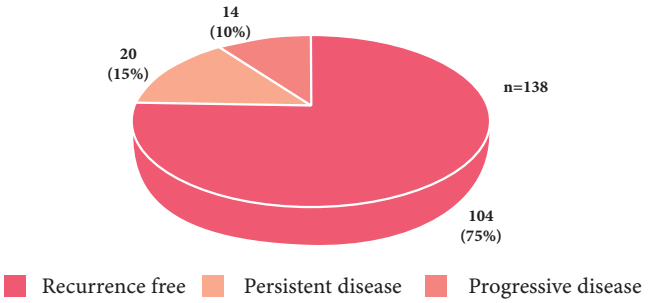

Figure 1: Recurrence–free rates of patients to intravesical BCG at 5 years

were evaluated, with a median age of 60 years (range 32 – 75 years). Seven patients had pTa disease, with four having low grade disease and three having high grade disease. T1 low grade disease affected 88 patients, while T1 high grade disease affected 43. So far, 104 patients (75%) have had no recurrences, 20 patients (14.5%) have had persistent disease, and 14 patients (10%) have had progressive disease (Figure 1). The mean length of follow-up is 82.5 months (range: 23–144 months).

The most common treatment-related side effects were cystitis, haematuria, and urinary tract infection. Cystitis was reported by 122 patients (88%), microscopic haematuria by 21 patients (15%), intermittent gross haematuria by 3 patients (2%) and urinary tract infection by 8 patients (6 percent)

Patients who developed recurrent disease or progression were discussed in Urology Multi disciplinary meeting (MDT) and were given a trial of re induction after complete TURBT. Out of 34 patients, 32 received re induction BCG while 2 were offered cystectomy due to extent of disease but both never underwent cystectomy. Out of 32 patients receiving re induction BCG, 24 patients had completed re induction and maintenance BCG while remaining 8 patients were discussed in Urology MDT for salvage cystectomy. 3 out of 8 patients underwent salvage cystectomy while 5 declined cystectomy and were placed on follow up.

DISCUSSION

Non-muscle invasive bladder cancer (stage Ta, Tis, or T1) is initially treated with TURBT. Several factors influence the risk of recurrence and progression. These tumours should be grouped according to the table 1. Table 2 displays the percentages based on tumour grade and stage. The European Organization for Research and Training in Cancer has created a calculator that takes into account prior recurrence rate, number of tumours, tumour diameter, tumour stage, tumour grade, and concomitant Cis [10].

Non-muscle invasive bladder cancer has a recurrence rate of 60 – 80 percent if left alone after transurethral resection of bladder tumour (TURBT) [2,3]. Our data suggests that the recurrence rate in our patient population is similar to the rates reported in western literature. Intravesical mitomycin is the standard treatment for pTa after TURBT, while intravesical BCG is used for Tis, HG and pT1[11,12]. Patients who develop a recurrence of disease while on maintenance therapy are given a trial of re-induction therapy. A second recurrence necessitates radical cystectomy, which the majority of patients are hesitant to undergo. In our patient population , only 3 patients underwent cystectomy while the rest i-e at least 7 patients had declined the procedure. At this point, the vast majority of these patients are lost to follow-up, and they only return when they have locally advanced or metastatic disease. Prospective trials have shown that intravesical BCG is superior to any systemic chemotherapy for pT1 disease [13-15]. Low risk group patients benefit from a single intravenous instillation of Mitomycin, according to a consensus among urologists and oncologists based on the EORTC and MRC trials [15-17]. Intravesical BCG should be administered to intermediate and high-risk patients following TURBT, according to the SWOG/MRC protocol. The best BCG protocol has yet to be determined, but the recommendations are for 2–3 years. According to van der Meijden et al., the majority of high grade pT1 (pT1G3) tumours recur, whereas BCG extended time to recurrence but not time to progression when compared to Epirubicin [18].

CONCLUSION

BCG remains the treatment of choice for high-risk disease. There is evident reluctance on part of patients to undergo salvage cystectomy once the BCG fails.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

DISCLOSURE

This article has not been submitted for publication to any other journal. Updates on the study, however, have been presented orally at national Oncology/Urology conferences.

AUTHORS' CONTRIBUTION

Abdus Samad Syed	Conception and design, Critical revision
Fauzia Abdus Samad	Analysis and interpretation of data, Drafting the Article
Sameed Hussain	Acquisition of data

REFERENCES

1. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018 Jan;68(1):7-30. doi: 10.3322/caac.21442. Epub 2018 Jan 4.
2. Kiemeney LALM, Witjes JA, Verbeek ALM, Heijbroek RP, Debruyne FMJ. The clinical epidemiology of superficial bladder cancer. Br J Cancer 1993;67:806-12.
3. Lamm DL, Griffith JG. The place of intravesical chemotherapy as defined by results of prospective randomized studies (substances and treatment schemes). Prog Clin Biol Res 1992;378:43-53.
4. Morrison DA, Murphy WM, Ford KS, Soloway MS. Surveillance of stage 0 grade 1 bladder cancer by cytology alone: is it acceptable? J Urol 1984; 132:672-4.
5. Lamm DL, Long-term results of intravesical therapy for superficial bladder cancer. Urol Clin North Am 1992;19:573-80.
6. Pawinski A, Sylvester R, Kurth KH, Bouffioux C, Van der Meijden A, Parmer MK, et al. A combined analysis of EORTC and MCR randomized clinical trials forthe prophylactic treatment of TaT1 bladder cancer. J Urol 1996;156:1934-40.
7. European Association of Urology Guidelines 2017. Available at http://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/#6. Accessed on 8 Sep 2018.
8. Pawinski A, Sylvester R, Kurth KH, Bouffioux C, van der Meijden A, Parmar MK, et al. A combined analysis of European Organization for Research and Treatment of Cancer, and Medical Research Council randomized clinical trials for the prophylactic treatment of Stage TaT1 bladder cancer. J Urol 1996;156:1934-41.
9. Cancer Therapy Evaluation Program. (1999, April 30). Common Toxicity Criteria. Retrieved April 20,2012, from eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf
10. Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, 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. Eur Urol

2006;49: 466 - 477.

11. Sylvester RJ, Oosterlinck, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer. A meta analysis of published results of randomized clinical trials. J Urol 2004;171:2186-2190, quiz 2435.
12. Bladder Cancer. (2011, December 22). Montei JE, Clark PE, Agarwal N, et al. NAtional Comprehensive Cancer Network. Retrieved April 17, 2012 from nccn.org/professionals/physician_gls/pdf/bladder.pdf
13. Herr HW, Schwalb DM, Zhang ZF, Sogani PC, Fair WR, Whitmore WF Jr, et al. Intravesical bacillus Calmette–Guérin therapy prevents tumor progression and death from superficial bladder cancer: ten-year follow-up of a prospective randomized trial. J Clin Oncol 1995;13:1404–8.
14. Pawinski A, Sylvester R, Kurth KH, Bouffioux C, van der Meijden A, Parmar MK, et al. A combined analysis of European Organization for Research and Treatment of Cancer and Medical Research Council randomized clinical trials for the prophylactic treatment of stage TaT1 bladder cancer. European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council Working Party on Superficial Bladder Cancer. J Urol 1996;156: 1934–40.
15. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, et al. Maintenance bacillus Calmette–Guérin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000; 163:1124–9.
16. Isbarn H, Budäus L, Pichlmeier U, Conrad S, Huland H, Friedrich MG. Comparison of the effectiveness between long-term instillation of mitomycin C and short-term prophylaxis with MMC or bacille Calmette-Guérin. Study of patients with non muscle-invasive urothelial cancer of the urinary bladder. Urologe A. 2008;47:608-15.
17. Volpe A, Racioppi M, D'Agostino D, Cappa E, Filianoti A, Bassi PF. Mitomycin C for the treatment of bladder cancer. Minerva Urol Nefrol. 2010;62(2):133-44.
18. van der Meijden AP, Brausi M, Zambon V, Kirkels W, de Balincourt C, Sylvester R. Members of the EORTC Genito-Urinary Group. Intravesical instillation of epirubicin, bacillus Calmette–Guérin and bacillus Calmette–Guérin plus isoniazid for intermediate and high risk Ta, T1 papillary carcinoma of the bladder: a European Organization for Research and Treatment of Cancer genito-urinary group randomized phase III trial. J Urol 2001;166:476–81.