Original article

Comparison of Adjuvant Intravesical Chemotherapy and Immunotherapy In Superficial Transitional Cell Carcinoma Of Urinary Bladder

[1]DR. SINGHAL S, [2]DR. ARORA PK, [3]DR. TIWARY BN, [4]DR. MARBATE ST, [5]DR. DR. MALIK P.

[1]Additional Chief Health Director and Head Of the Department-Surgery/NRCH

[2, 3]Senior Divisional Medical Officer(SG) and Head of Unit/ Surgery/NRCH

[4]DNB Resident/ Surgery

[5]Divisional Medical Officer and Head of Unit/ Surgery/NRCH

Department Of Surgery, Northern Railway Central Hospital, Basant Lane, New Delhi-110055, Mobile- 9717630538

Name of the Institute/college: NORTHERN RAILWAY CENTRAL HOSPITAL

Corresponding author: DR PANKAJ KUMAR ARORA

Abstract

This is a prospective case series, in which the outcome of post operativeintravesical chemotherapy and immunotherapy was evaluated and compared in patients with superficial (T_a/T_1) transitional cell carcinoma urinary bladder. From January 2016 to December 2018, 20 patients of superficial transitional cell carcinoma urinary bladder were entered into the study. The criteria for inclusion were patients with Ta and T1 superficial TCC without CISTransitional cell carcinoma of urinary bladder. The mean age of the patients was 66.15 ± 9.73 SD years (range: 43 to 80). All patients underwent TURBT followed by intravesical instillation of weekly dose of either BCG or MMC starting from six weeks following TURBT. The patients were followed up with 3 monthly urinary, radiological and cystoscopicinvestigations.The minimum follow up was 1 year. The results of the study showed that both BCG and MMC have comparable efficacies with respect to recurrence at 1 year follow up, while side effects are more commonly seen in the BCG group. In the present study, BCG was found to be 90% recurrence free while as MMC showed a recurrence of 20%. The side effects are marginally higher in the BCG group with 70% of patients having cystitis as compared to 40% in the MMC arm but the side effects were mild and did not require any delay or cessation of therapies.Also it was observed that there is no progression in the grade of the recurrence observed after intravesical therapy.

Key words: intravesical therapy; immunotherapy; superficial TCC; CIS; BCG; MMC; recurrence; toxicity.

INTRODUCTION

Bladder cancer is one of the most common diseases treated by Urologists, the second most common cancer of the genitourinary tract. It is the fourth most common carcinoma in men after prostate, lung and colorectal cancers; and the eighth most common cancer in females[1]. Superficial bladder cancer is a commonly encountered urological malignancy because of its high incidence and recurrence rates with five year recurrence rates between 30 to 66%. Risk factors for recurrence being more than one tumour, large (>3cm), high grade, or superficially invasive (pT1) tumours[2].

There has been a considerable change in the treatment for superficial bladder cancer. From the early days of repeated electro-coagulation in the 1950's to intravesical chemotherapy using thiotepa in 1960's[3] and

intravesical immunotherapy using BCG in the 1970's and 80's[4], the treatment options have been revolutionised. The need for intravesical treatment evolved in order to prevent tumour recurrence after successful local surgical resection. For years various intravesical chemotherapeutic agents such as thiotepa, doxorubicin and mitomycin have been the mainstay of therapy, but although they achieved short remissions, a net durable benefit was only apparent in 7 to 14% of patients[5,6] The disappointing results with chemotherapy and also radiotherapy set the stage for the induction of more unconventional forms of therapy, such as immunotherapy.

In the present study, we report the outcomes in a case series of patients with superficial transitional cell carcinoma of urinary bladder.

PATIENTS AND METHODS

Between January 2016 and December 2018, we treated about 28 patients of patients with TCC of urinary bladder. 20 were superficial, 3 invasive and rest had metastatic disease. All patients were subjected to a battery of tests and histopathological diagnosis was confirmed including the depth and grade of the disease. 20 patients were included from the superficial TCC group. These patients were subjected to TURBT followed by instillation of intravesical agents. The average age of the patients was 66.15 ± 9.73 SD years (range: 43 to 80). The male to female ratio was 1:6.3. All the patients presented to Surgical OPD/ Casualty Northern Railway Central Hospital, New Delhi with complaints of painless hematuria. All patients underwent routine laboratory investigations followed by some special investigations including urinary cytology for 3 consecutive days, NMP 22 check for 2/3 days, Chest roentgenogram, US abdomen, CT abdomen and bone scan. Patients underwent cystoscopic biopsy and histopathological confirmation. All patients with superficial bladder cancer were subjected to TURBT after anaesthetic clearance. All patients received intravesical MMC (40mg) in immediate postoperative period. All patients with Ta and T1 superficial TCC were selected and included in the study. Patients were randomly distributed into two arms. Patients received six weekly cycles of either intravesical BCG (120mg) or Mitomycin C (40mg) starting from six weeks after initial TUR or fulguration of bladder tumor. Thereafter patients received further maintenance doses at 3 month intervals for the next year. During the study the selected patients were followed for a minimum period of one year and the patients evaluated for recurrence at three monthly intervals by CBC, routine urine examination, urine cytology for 3 days, NMP-22, ALP, USG abdomen and cystoscopy and chest radiograph and CT abdomen at six month interval.

RESULTS

Three patients receiving intravesical therapy had recurrence of the disease. One had recurrence at 3 month follow up and the rest two were diagnosed with recurrent growth at 6 month follow-up. 7 out of ten patients in the BCG arm had side effects ascompared to 4 in the MMC group. Cystitis was the most common complication in either group.

The patients of the study group i.e. the 20 patients of superficial bladder cancer underwent TURBT. Postopertively they were randomly divided into 2 groups with comparable age distribution. *Graph* 1

RECURRENCE

Patients were kept in follow up and assessed at 3 monthly intervals for a period of one year. Assessment was based on urinary tests i.e. urinary cytology and NMP 22, ultrasonography, radiology and cystoscopy. One recurrence was observed at 3 month follow up. 2 more recurrences were observed at the end of 6 months. Out of the 3 recurrences 2 were observed in MMC group and 1 in BCG group (p= 0.39474). Preoperatively all tumours

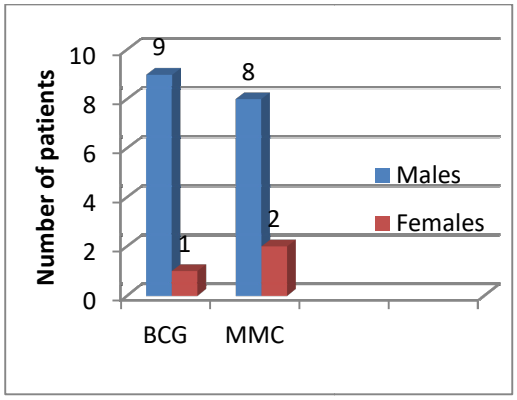
were grade II and the tumour recurrence was also of the same grade in all the three and therefore no progression of disease was observed in the study.(*Table* 1) (*Graph*2)

SIDE EFFECTS/ TOXICITY

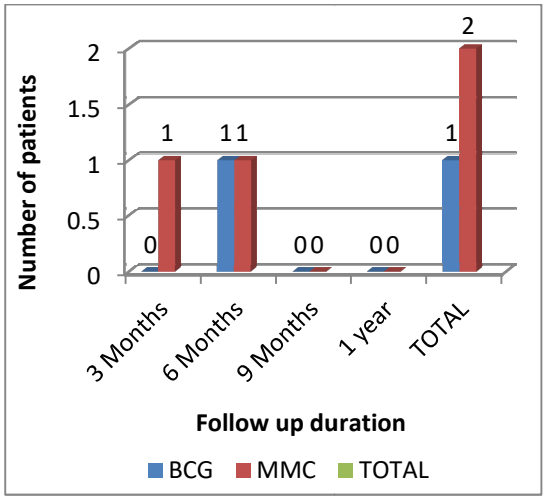
Following TURBT after 6 weeks all the patients were started with weekly intravesical therapy receiving either BCG or MMC for a period of 6 weeks. The patients were evaluated for any local or systemic side effects of the intravesical therapy. Side effects were more common in the BCG group. Seven out of 10 patients on BCG immunotherapy experienced side effects whereas only 4 of those receiving MMC had complaints (p= 0.15004). Cystitis was the most common side effect observed. *Graph 3*

Symptoms observed were generally mild and any delay or cessation of the therapy was not required. One patient in the BCG group developed severe cystitis requiring admission and was started on anti tubercular therapy. None of the patients developed any allergic reaction. Three patients in the BCG group developed fever after instillations easily controlled by antipyretics. There were no deaths associated with the therapies.

Graph 1: Patient characteristics



Graph 2: Comparison of recurrence rates in the study groups



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Graph 3: Comparison of toxicity in the study groups

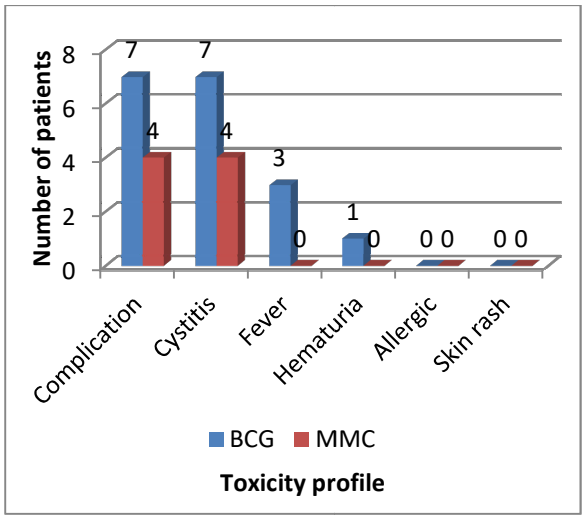

Table 1: Recurrences in follow up

	BCG	MMC
Number of patients	**10**	**10**
Recurrence at 3 Months	**0**	**01**
Recurrence at 6 Months	**01**	**01**
Total	**01**	**02**

Table 2: Disease free percentage in follow up in previous studies

Study (follow up period)	**6 months**		**12 months**		**At the end of study**	
	BCG	MMC	BCG	MMC	BCG	MMC
DeBruyne et al (2 years)	-	-	-	-	58	64
Rintala et al (2 years)	88	70	90	67	97	79
Lundholm et al (3 years)	90	90	65	58	49	34
Maelstrom et al (5 years)	90	90	65	55	47	34
Present study (1 year)	**90**	**80**	**90**	**80**	**90**	**80**

DISCUSSION

Superficial bladder cancer has been notorious for a high recurrence rate. Treatment for superficial bladder cancer has undergone a revolution from early days of repeated electrocoagulation to intravesical chemotherapy and then to immunotherapy using intravesical BCG. The intravesical therapy evolved out of need to prevent tumour recurrence after successful surgical resection. Immunotherapeutic and chemotherapeutic agents can be instilled into bladder, thereby avoiding the morbidity of systemic administration. Intravesicaltherapy can have a prophylactic or therapeutic objective. Adjuvant intravesical chemotherapy or immunotherapy is indicated in

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patients who are at high risk for tumor recurrence by virtue of having multiple tumors, recurrent tumors, high grade tumors associated with urothelial atypia or CIS[7]. When instilled immediately following TURBT, it acts prophylactically to reduce implantation.[8]

Post TURBT intravesical chemotherapy using various agents like thiotepa, doxorubicin and mitomycin C has been the mainstay of treatment. These agents have achieved short remissions, a net durable benefit being apparently in only 7% to 14% of the patients[5,6]. Intravesical immunotherapy with agents such as BCG has become an important treatment modality, although there has been a difference of opinion with regards to its superiority over chemotherapeutic agents such as MMC.

Intravesical chemotherapy began in 1960's with the introduction of intravesical thiotepa.[9]Beforethiotepa other agents used were silver nitrate, trichloroacetic acid and podophyllin. Various agents used for intravesical instillation for treatment of TCC urinary bladder include thiotepa (Triethylenethiophosphoramide), etoglucid (Epodyl), doxorubicin/adriamycin, epirubicin, mitomycin C and BCG.

Mitomycin C is an antitumor, antibiotic, alkylating agent that inhibits DNA synthesis and is effective as primary treatment of previously untreated bladder tumors and has been shown to be effective in patients who have failed prior treatment with thiotepa[10,11,12]. Approx 1% of instilled Mitomycin C is absorbed[13]. Between 39-78% of patients with residual tumor experience a complete response to intravesical MMC[14] and recurrence is reduced in 2-33% after complete TUR[15]. A study conducted by the National Bladder Cancer Group (NBCG) involved treatment with 40 mg MMC for 8 consecutive weeks which concluded that 36% of the patients had complete response. The NBCG also compared MMC and thiotepa showing that MMC had a statistically significant higher complete response rate(39% versus 27% against thiotepa; p= 0.02). Side effects are noted in 10-43% of patients and consist largely of irritative voiding symptoms including frequency, urgency and dysuria. Chemical cystitis (10-15%) may lead to bladder contraction, mural calcification[16] and skin rashes over palms and genitalia (5-15%).

Immunotherapy came up as a treatment modality for carcinoma bladder due to the disappointing results with chemotherapeutic agents. Few agents have been used for immunotherapy in bladder cancer which include BCG, Keyhole Limpet hemocyanin and interferon-α. BCG is an attenuated strain of *Mycobacterium bovis* that has stimulatory effect on immune responses. The exact mechanism by which BCG exerts its antitumor effect is unknown, but it seems to be immunologically mediated. BCG has shown to be very effective both therapeutically and prophylactically. It appears to be the most efficacious intravesical agent for the management of CIS. Regardless of its actual target, intravesical BCG therapy clearly exercises some of its antitumor effects through immune mechanisms[17,18]. BCG induces a chronic granulomatous response in bladder of many patients[19,20,21,22]. Complete responses are recorded in 36-71% of patients with residual carcinoma[15,17]. Recurrence rates are reduced substantially in patients treated after TURBT (11-22%) versus a 70% recurrence after endoscopic resection alone[23].

Several studies have demonstrated significantly greater efficacy of BCG than thiotepa[24]and Mitomycin C[25]. Bladder instability is the main side effect of BCG therapy. It can be relieved to some extent by oral Oxybutyrin 50mg thrice daily and Phenazopyridine 200mg TDS. The complex includes dysuria (91%); frequency (90%); hematuria (46%); fever (24%); malaise (18%); nausea (8%); chills (8%); arthralgias (2%) and pruritis (1%).

In the present study BCG and MMC were compared with respect to efficacy of the therapy in prevention of recurrences following definitive TURBT in superficial bladder cancer and side effects to the therapy. All agents for intravesical chemotherapy are about equally effective[26]. When used as prophylaxis against tumor recurrence, recurrence rates have been reduced to 30-44% compared with about 70% in controls.

In previously conducted studies, the disease free percentages at one year follow up period varied from 65% to 90% for BCG and 55% to 67% for MMC following TURBT in superficial bladder cancer. The disease free percentage showed a downward trend over the years with results mostly in favour of BCG.*Table2*

In our study recurrence was observed in 1 case at 3 month follow up and 2 more cases at 6 month follow up, with 2 recurrences in MMC group and 1 recurrence in BCG group. Statistically p value for this observation is 0.39474 and the Pearson's chi-square corresponds to 0.392 (p= 0.531168). There was no progression of the grade of disease in the recurrent tumour.

The disease free percentage at 1 year follow up in our study is 90% for BCG therapy and 80% for MMC therapy. In our study, each group comprised of 10 patients. The number of patients in both the study arms is small it can be summarised that both the study groups have comparable results and are equally efficacious at 1 year follow up taking into account both the recurrence rates and toxicity profile in both limbs. These values correlate with other studies (*Table 2*) that also shows comparable results between BCG and MMC at 1 year follow up.

Further follow up in these studies predominantly favour BCG. De Bruyne et al, conducted their study in 1985 and their 2 year follow up study did not show any statistically significant difference in the disease free percentage of BCG and MMC study arms. Malmstrom et al in their 5 year follow up study conducted in the early nineties showed BCG to have a disease free percentage of 47% and MMC of 34%, which is a significant difference. Similar results have been quoted by Lundholm et al in their 3 year follow up study conducted in the early nineties. The studies conducted in recent years have favoured BCG. To comment on this in our study a further follow up is required.

Although a significant difference has been observed in these studies between BCG and MMC, no significant difference has been observed with respect to progression of disease and survival[108(27)]. A formal meta-analysis of comparative studies on recurrence and toxicity suggested superiority of BCG over Mitomycin C for prevention of tumor recurrences in the combined data and particularly in the BCG maintenance treatment subgroup, irrespective of the actual tumor risk status. The toxicity with BCG is higher but does not differ between BCG maintenance and non maintenance groups[28].

A 5 year follow up of a randomised study comparing MMC and BCG in 250 patients with superficial bladder cancer found BCG to be superior to MMC for recurrence prophylaxis. No difference in tumour progression and crude or corrected survival was found between the two.[29]

Side effects of the therapy were divided into local, allergic and systemic. Local side effects were observed in both the study arms. In our study, patients in the BCG group had more local side effects (70%), which included cystitis, hematuria and acute retention of urine when compared to the MMC group. In our study, the values for 'p' and Pearson's chi-square for these observations equal 0.15004 and 1.818 (p= 0.17753).

Cystitis following BCG instillation occurs due to a marked immune response in the bladder wall. BCG interacts with the urothelial cells that produce a leucocyte response. These leucocytes secrete cytokines that activate other

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immune cells. All these lead to a marked tissue response that manifests as cystitis. MMC generally produces a chemical cystitis but may produce a bacterial cystitis also due to secondary infection. In our study the patients were categorised as suffering from cystitis when they complained of burning micturition, dysuria and increased frequency of micturition. Four of the patients receiving MMC therapy (40%) and 7 receiving BCG (70%) developed cystitis. Most of these patients developed complaints after every dose and lasted for 24 to 48 hours, except for one patient who developed severe cystitis and was admitted and managed with parenteral medications.

Witjes et al in a study comparing MMC (30 mg) and BCG (120 mg) reported cystitis in 36% of MMC group and 57% of BCG group. These values are comparable to the values obtained in our study. De Bruyne et al and Rintala et al reported cystitis in 21% and 3.5% of the patients in the MMC group (20 mg) respectively while both reported cystitis in 18% of patients receiving BCG therapy (75 mg). Krege et al reported cystitis in 36% and 16% in BCG (120 mg) and MMC (40 mg) therapies respectively, while Lundholm et al reported cystitis in 70% of patients receiving MMC (40 mg) and 80% of patients receiving BCG therapy(120 mg). In general the percentage of cystitis as observed in the above studies seems to be directly proportional to the dose of the drug given in either of the two arms.

Hematuria is a known complication of intravesical therapy. It generally develops as a result of granulomatous cystitis but may also be due to destruction of visually detectable tumour. Malmstrom et al and Martinez Pinerio et al in their studies have reported hematuria in 12% of the patients and Ali el-dein et al reported hematuria in 7% of the patients receiving BCG therapy whereas Lundholm et al is the only study that reported a high incidence of hematuria (90%) and they have not offered any acceptable reason of this high incidence of hematuria following BCG therapy. In our study hematuria was observed in one patient (10%) in the BCG group.

No allergic reactions were observed in either of the study groups. Allergic reactions occur due to hypersensitivity to the intravesical agent. In one study conducted by DeBruyne et al, out of a total population of 338 patients, allergic reactions were encountered in 2% of patients in BCG group and 8% of patients in the MMC group.

Fever was the only systemic side effect that was observed. Three patients (30%) in the BCG arm developed fever after almost every dose instillation. Fever was low grade accompanied with malaise. Patients were treated with antipyretics and responded well. Fever develops due to passage of BCG bacilli into the intravascular compartment. Persistent high grade fever if present may be the first sign of severe systemic side effects such as pneumonitis, granulomatous hepatitis or BCG sepsis. In such cases, therapy should be stopped and the patients started on isoniazid or rifampicin therapy. None of the patients in our study developed such complications. Lundholm et al in their study observed fever in 6% of the patients in the MMC group and 24% of the patients in BCG group. Pagano et al reported fever in 28% of the patients in the BCG group. Both these studies have used standard dose BCG (120 mg). Martinez-Pinerio et al reported fever in only 2% of the cases while using low dose (81 mg) BCG therapy. Our study correlates well with the studies previously conducted with standard dose therapy.

One side effect that has been mentioned in MMC studies has been skin rashes due to contact dermatitis. Skin rashes in the genital region and the hands have been reported very commonly (upto 50%) in the patients. There

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were no such observations in our study. The reason for this being that the patients were instructed to wash their hands and genital area with soap and water after each act of micturition for next 48 hours.

From the above discussion it can be concluded that both BCG and MMC have comparable efficacies with respect to recurrence at 1 year follow up, while side effects are more commonly seen in the BCG group. In the present study, BCG was found to be 90% recurrence free while as MMC showed a recurrence of 20%. The side effects are marginally higher in the BCG group but mild and did not require any delay or cessation of therapies. When compared and analysed with other series of 2 to 5 years follow up, BCG therapy has been found to be superior to MMC. Since recurrence is the most important factor in the management of superficial bladder cancer, while comparing intravesical therapies, the higher rates of these mild toxicities with BCG therapy is acceptable.

BIBLIOGRAPHY

1) Boring CC, Squires TS, Tong T, et al. Cancer statistics-1995. *Cancer J Clin*1995; 45: 2
2) Lang P, DeBruyne F, Fradet Y, Narayan P. Symposium: Treating superficial bladder cancer. *ContempUrol*1996; 8: 61
3) Jone HC, Swinney J. Thiotepa in the treatment of tumours of the bladder. *Lancet* 1961; 2: 615
4) Lamm DL, Thor DE, Harris SC, et al: BCG immunotherapy of superficial bladder cancer. *J Urol* 1980; 124: 38
5) Pawinsky A, Sylvester R, Kurth KH, et al: A combined analysis of European Organisation for Research and Treatment of Cancer, and Medical Research Council: randomized trials for the prophylactic treatment of stage TaT1 bladder cancer. *J Urol* 1996; 156: 1934
6) Lamm DL, Riggs DR, Traynelis CL, Nyeso UO. Apparent failure of current intravesical chemotherapy prophylaxis to influence the long term course of superficial transitional cell carcinoma of the bladder. *J Urol* 1995; 153: 1444
7) Rubben H, Lutzeyer W, Fischer N, et al. Natural history and treatment of low and high risk superficial bladder tumors. *J Urol* 1988; 139:283
8) Solsona E et al. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: Short and long term follow-up. *J Urol* 1999;161:1120
9) Jones HC, Swinney J. Thiotepa in the treatment of tumors of bladder. *Lancet* 1961; 2:615
10) Prout GR Jr, Griffin PP, Nocks BN, et al. Intravesical therapy of low stage bladder carcinoma with mitomycin C: Comparison of results in untreated and previously treated patients. *J Urol* 1982; 127:1906
11) Stricker PD, Grant AB, Hosken BM, et al. Topical mitomycin C therapy for carcinoma of the bladder. *J Urol* 1987; 138:1164
12) Issell BF, Prout GR Jr, Soloway MS, et al. Mitomycin C intravesical therapy in noninvasive bladder cancer after failure of thiotepa. *Cancer* 1984; 53:1025
13) Van Helsdingen PJ, Rikken CH, Sleeboom HP, et al. Mitomycin C resorption following repeated intravesical instillations using different instillation times. *UrolInt* 1988; 43:42
14) Kowalowski TS, Lamm DL.Intravesical chemotherapy of superficial bladder cancer. In: Resnick M (editor): *Current Trends in Urology.* Williams & Williams, Philadelphia, PA, 1988
15) Herr HW, Laudone VP, Whitmore WF. An overview of intravesical therapy for superficial bladder tumors. *J Urol* 1987;138:1363

16) Drago PC, Badalament RA, Lucas J, Drago JR. Bladder wall calcification after intravesicalmitomycin C treatment of superficial bladder cancer. *J Urol* 1989; 142:171

17) Catalona WJ, Ratliff TL. Bacillus Calmette-Gue'rin and superficial bladder cancer: Clinical experience and mechanism of action. *Surg Ann* 1990; 22:363

18) Kavoussi LR, Brown EJ, Ritchey JK, et al. Fibronectin-mediated Calmette-Gue'rin bacillus attachment to murine bladder mucosa. *J Clin Invest* 1990; 85:62

19) Morales A, Eidinger D, Burse AW. Intracavitary Bacillus Calmette- Gue'rin in the treatment of superficial bladder tumors. *J Urol* 1976; 116:180

20) Lamm DL, Thor DE, Harris SC, et al. Bacillus Calmette -Gue'rin immunotherapy of superficial bladder cancer. *J Urol* 1980; 124:38

21) Schellhammer PF, Ladago LE, Fillion MB. Bacillus Calmette-Gue'rin (BCG) for superficial transitional cell carcinoma (TCC) of bladder. *J Urol* 1986; 135:261

22) Torrence RJ, Kavoussi LR, Catalona WJ, et al. Prognostic factors in patients treated with intravesical Bacillus Calmette-Gue'rin for superficial bladder cancer. *J Urol* 1988; 139:941

23) Catalona WJ, Ratliff TL. Bacillus Calmette Guerin and superficial bladder cancer: Clinical experience and mechanism of action. *Surg Ann* 1990; 22:363

24) Brosman SA. Experience with bacillus Calmette-Gue'rin in patients with superficial bladder carcinoma. *J Urol* 1982; 125:196

25) Lamm DL, Blumenstein BA, Crawford ED, et al. Randomised intergroup comparison of bacillus Calmette-Guerin immunotherapy and mitomycin C chemotherapy prophylaxis in superficial transitional cell carcinoma of urinary bladder. *UrolOncol*1995a; 1:119

26) Newling D. Intravesical therapy in the management of superficial transitional cell carcinoma of the bladder: Experience of the EORTC group. *Br J cancer* 1990; 61:497

27) Lundholm C, Norlen BJ, Ekman P, et al. A randomized prospective study comparing long term intravesical instillations of mitomycin C and BCG in patients with superficial bladder cancers. J *Urol 1996*; 156:372

28) Bohle A, Jocham D, Bock PR. Deptt of Urology, Medical Univ of Lubeck, Germany. Intravesical BCG vs Mitomycin C for superficial bladder cancer: A formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol*2003 Jan;169(1);90-5

29) Per-Uno Malmstrom, Hanswikstrom, Lundholm C, et al. Five year follow up of randomised prospective study comparing mitomycin C and BCG in patients with superficial bladder cancers. *J Urol* 1992; 161:1124