SUPERFICIAL BLADDER TUMOR;

Effectiveness of single dose perioperative mitomycin-c instillation in reducing recurrence

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ABSTRACT… Introduction: Bladder cancer is the second most common urologic cancer. Approximately 90% are transitional cell carcinoma among which superficial bladder cancer constitutes about 50-70%. It is usually treated by transurethral resection with adjuvant intravesical instillations of chemotherapy or immunotherapy. Primary problems in superficial bladder cancers are its tendency to recur, about 50-80%, following surgical ablation alone, with progression to muscle invasive disease in 20-25% cases. Intravesical chemotherapy appears to have major impact on decreasing chances of recurrence of superficial bladder cancer. **Objective:** To determine the efficacy of single dose perioperative intravesical mitomycin C in reducing recurrence of superficial bladder tumor. Study **Design:** Comparative study. **Settings:** Department of Urology Shaikh Zayed Hospital Lahore. **Duration of Study:** One year.13-04-2009 to 13-04-2010. **Methodology:** Patients were divided into two groups randomly by using random numbers i.e. 40 patients in group A and 40 patients in group B. Group A (40 patients) of bladder tumor received post TURBT single dose Mitomycin-C 40 mg/40ml N/Saline intravesically and Group B (40 patients) was control group i.e. TURBT alone without Mitomycin-C. **Results:** The recurrence at first year follow up in both groups were showed a significant difference ($p<0.05$) as shown in Table No V: There were only 10% recurrence in Group A i.e. patients who had intravesical Mitomycin –C as compared to 55% recurrence in Group B, who did not received postoperative intravesical Mitomycin–C. **Conclusions:** It is concluded that one perioperative (within 6 hours of TURBT) intravesical instillation of chemotherapy significantly decreases the risk of recurrence after TURBT in patients with stage Ta T1, single and multiple papillary bladder cancer in low risk as well as high risk tumors. One immediate instillation after TUR reduces the recurrence.

Key words: Superficial bladder tumor, Mitomycin –C, Perioperative TURBT.

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INTRODUCTION

Bladder cancer is the second commonest urological malignancy in the world. In United States in year 2006, 61420 new cases were diagnosed. Majority of bladder cancers presents as superficial transitional cell cancers[1]. Average age at diagnosis is 65 years, at that time approximately 75% bladder cancer are localized 25% have spread to regional lymph nodes or distant sites. Approximately 90% are transitional cell carcinoma, adenocarcinoma <2% (may be precede by cystitis) and squamous cell carcinoma constitutes 5-10% (associated with history of chronic infections, vesical calculus or longstanding indwelling catheterization; it is also associated with Bilharzias' infection, (schistosoma hematobium). Among transitional cell carcinoma of bladder superficial bladder cancer constitute about 50-70%[2].

Transitional cell carcinoma may occur anywhere along urinary tract including renal pelvis, ureter, bladder and proximal 2/3 of urethra. More than 90% originate in bladder 8% in renal pelvis and 2% in ureter and urethra. At presentation 50-70% of bladder tumors are superficial, 20% are invasive and up to 5% have de novo metastasis. About 70% superficial bladder tumor are exophytic, papillary tumors confined to mucosa (pTa), 30% invade sub mucosa i.e. lamina propria (pT1). Superficial bladder tumors may be solitary or multifocal and may recur at the same site or at other site. It may recur as more advanced stage and grade[3]. The problem in superficial bladder cancer is its tendency to recur, about 50 to 80%, following surgical ablation alone. It may progress to muscle invasive disease in 20 to 25% cases[4] and have a high rate of recurrence in the first year following transurethral resection (TUR)[5].

Non muscle invasive bladder cancer after transurethral resection (TUR) is known to recur frequently, even in patients who receive intravesical chemotherapy or immunotherapy. Up to 70% of all non muscle invasive bladder cancer recur within 3 years if left untreated after TUR. More importantly there is progression to higher stage in 4-45% of recurrent tumors, which becomes potentially life threatening[6]. The high recurrence rate in superficial bladder cancer (>70%) is caused by the adhesion of free floating tumor cells during transurethral resection by incomplete resections and by overlooked and new tumors. Frequent follow-ups and reoperations are necessary[7]. It is usually treated by transurethral resection with adjuvant intravesical instillations of chemotherapy or immunotherapy. Adjuvant instillation therapy with chemo or immunotherapeutic agents is an integral component in the treatment of superficial bladder cancer[8].

Intravesical chemotherapy appears to have a major impact on decreasing chances of recurrence of superficial bladder cancer. Three year recurrence decreases as much as 70% following intravesical chemotherapy after TURBT when compare with TURBT alone[9]. Different chemotherapeutic drugs are available for intravesical instillation, one of them is Mitomycin–C, which is antibiotic alkylating agent. It has results in significant reduction in the number of recurrences when given intravesically post TURBT, it prevent tumor cell implantation on the site of resection and eliminate any residual disease[10]. A single immediate instillation of chemotherapy after TURBT is effective in reducing recurrence rates as much as 4.5% at one year as compared to 38.1% in patients with TURBT alone and it increases recurrence free interval[11]. One postoperative (within 6 hours of TURBT) intravesical instillation of chemotherapy significantly decreases the risk of recurrence in patients with stage Ta T1, single or multiple papillary tumors, in low risk as well as high risk tumors. Efficacy of mitomycin-C is optimum within 6 hours of resection. The usual optimal contact time of the drug is one hour[12,13,14].

OBJECTIVE

This study was conducted to determine the efficacy of single dose perioperative intravesical mitomycin C in reducing recurrence of superficial bladder tumor.

MATERIAL AND METHODS

This is a comparative study conducted in the Urology Department of Shaikh Zayed Hospital Lahore. Eighty patients were included in this study. They were divided into two groups; group A (single perioperative MMC) and group B (control). Each group comprised 40 patients. Patients having bladder growth on CT scan were included. Those patients who have muscle invasive growth or advanced diseases were excluded from the study. Before instillation of MMC it was assured that there was no perforation of bladder per operatively and no gross hematuria post operatively. After instillation, bladder catheter was clamped so that drug stays inside the bladder for one hour. Patients were asked to change his or her position on bed every fifteen minutes. After one hour catheter clamp was released and irrigation started .Group B was control group i.e. TURBT alone without any intravesical Mitomycin-C. Patients were advised to visit out-patient clinic with histology report of the resected specimen from bladder. Patients with superficial bladder tumor (confirmed on biopsy) were followed by check cystoscopy after every 3 months for one year to see the whether the recurrence did occur or not. Results of both groups were compared in terms of recurrence of bladder growth at the end of study after one year.

RESULTS

There were 40 patients in group A, and 40 patients in group B. The mean age of patients in group A was 53.3±12.9 and in group B it was 56.0±13.1. There were thirty male patients and ten female patients in group A while in group B twenty nine male and eleven female patients as shown in Table-I.

Variable	Group A (n=40)	Group B (n=40)
Age (years)	53.3 ± 12.9	56.0±13.1
Gender (M:F)	30 : 10	29 : 11

Table-I. Age and sex distribution

While cystoscopy for TURBT, it was noted that 65% were single tumors and 35% multiple tumors (>4 tumors considered multiple), in group A while in Group B it was the same percentage for single and multiple tumors. Regarding the tumor appearance on cystoscopy it was 90% papillary and 10% solid appearing tumors in both groups (Table-II).

Cystoscopy	Group A (n=40)	Group B (n=40)
Single	57.5%	65.0%
Multiple	42.5%	35.0%
Papillary	82.5%	90.0%
Solid	17.5%	10.0%

Table-II. Cystoscopic findings

After TURBT, the specimen was sent for histopathology. On histopathology some tumors turned out to be low grade i.e. 57.5% and 42.5% high grade in Group A. While in Group B 60% were low grade tumors and 40% were high grade tumors. Regarding the TNM staging the tumors with Ta stage were 65% and tumors with T1 stage were 35% in group A. Stage Ta tumors were 57.5% and stage T1 were 24.5% in Group B)Table-III.

Finding	Group A (n=40)	Group B (n=40)
Low grade	57.5%	60.0%
High grade	42.5%	40.0%
Ta	65%	57.5%
T1	35%	24.5%

Table-III. Pathological findings

DISCUSSION

Transitional cell carcinoma is the second most common malignancy of genitourinary tract and the second most common cause of death among the genitourinary tumors[15]. Worldwide an estimated 356,600 new cases of bladder cancer occur each year and, in terms of overall cancer frequency, it is ranked as ninth[16]. In recent decades the overall incidence of bladder cancer appears to be rising[17]. The highest incidence rates are generally found in industrially developed countries, particularly in North America and Western Europe, and in areas associated with endemic schistosomiasis in Africa and Middle East. Bladder cancer is more common in men than women, with a worldwide male/female ratio of 10:3[13]. About 70-85% of transitional cell carcinomas of the bladder do not invade muscularis propria and they are currently defined as non-muscle invasive bladder tumours (confined to the mucosa or lamina propria)[18,19]. Patients with a high tumor grade, lamina propria invasion or associated carcinoma in situ (CIS) are considered to be groups of patients at high risk of progression. Thirty percent of patients with stage T1 and up to 78% of patients with diffuse CIS, progress to muscle-invasive or metastatic disease. Between 40% and 80% will present recurrence within 12 months after TUR of a non-muscle invasive and approximately 50% in the second year, being the risk of progression to muscle-invasive from 5 to 30% after 5 years[20].

	Recurrence (yes)		Recurrence (no)		P value
Group A	4	10%	36	80%	0.000
Group B	22	55%	18	45%	

Table-IV. Recurrence rate

The overall rate of recurrence is estimated to be 60-90% and the rate of progression is 10-30%. The probability of recurrence for Ta tumors is up to 50%, while for T1 tumors it is over 70%. As for grade, low grade tumors (G1-G2) have recurrence rates of close to 50-60%. Up to 80% of G3 or high-grade tumors will recur and nearly 50% will suffer disease progression[21].

The standard of treatment for patients with superficial bladder cancer is surgical transurethal resection (TUR) of tumors, with an 80% early success rate. However, nearly 70% of these patients will develop tumor recurrence, with 25% showing progression to muscle-invading disease, within 5 years with TUR[22].

Following TUR of a transitional cell bladder carcinoma, the period of high risk for the initial recurrence occurs within the first 2 years. Perhaps the most important factor responsible for early postoperative bladder recurrence in patients with non-muscle-invasive tumors is implantation of cancerous cells during resection. The unacceptable high recurrence rate after TUR has driven the search for supplementary treatments for NIMBC. A recurrence can be the result of either a true reappearance of a previously resected tumor or the development of a new primary tumor from genetically unstable urothelium[23]. Unfortunately in clinical practice, it is impossible to distinguish between two types of recurrence. True recurrence is probably most often the result of incomplete TUR, another possible mechanism is tumor cell implantation at the time of TUR. TUR of a non-muscle-invasive bladder carcinoma, immediate instillation of chemotherapy should be generally recommended to all patients, since it may reduce the risk of recurrence to nearly 50% at 2 years and more than 15% at 5 years[13,24].

Non-muscle-invasive baldder cancers are characterized by a favorable biological behavior with a specific survival superior to 90% and a life expectancy comparable to that of the population of similar age. However, their high recurrence rate leads to a reduction in quality of life because they require repeated treatments and periodic checkups. Although in modest but significant percentages, these superficial tumors can progress to muscle-invasive tumors, with the consequent threat for specific survival. Therefore, the use of intravesical treatments would be justified by a two-fold goal: to reduce the rate of recurrence and to prevent disease progression[25].

The best approach is to classify superficial bladder tumors into risk groups according to stage and grade so that more or less homogeneous biological behaviors can be differentiated and different treatments applied to each group[26].

Low risk bladder tumors, classified as single TaG1 tumors $\leq$3 cm in diameter, have a probability of recurrence at 1 year and 5 years of 15-24% and 31-46%, respectively, and a probability of progression of less than 1% and 1-6%, respectively[27] TUR alone is still the standard treatment for low-risk patients, e.g., patients with a single bladder carcinoma[28]. Transurethral resection of a bladder tumor alone has been recommended for low risk patients, but the substantial recurrence rates affected even the low risk patients because they subsequently underwent TUR-Bt again. Recently, some studies have revealed that a single instillation immediately after TUR-Bt prevents recurrences.

Intravesical chemotherapy and immunotherapy are widely used as adjuvant therapies after TUR, to prevent recurrence and progression of superficial disease. Systemic therapy is typically reserved for higher stage, muscle-invading, or metastatic diseases. The urinary bladder is an ideal organ for regional therapy. The urethra provides easy access of therapeutic agents to the urinary bladder. The presence of the specialized asymmetric unit membrane on the urothelium serves as a barrier and limits the absorption of molecules or particulates into the systemic circulation. For most

small molecule drugs, less than 5% of the dose is absorbed into the systemic circulation[29].

Immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer. Intravesical Mitomycin C can be optimized to significantly enhance its efficacy. Intravesical Bacillus Calmette-Guérin (BCG) appears to be the treatment of choice for the management of carcinoma in situ, and is superior to Mitomycin C in reducing tumor recurrence in high-risk nonmuscle-invasive bladder cancer. In addition, intravesical BCG significantly reduces the risk of progression after transurethral resection in patients with nonmuscle-invasive bladder cancer who[30]. Both MMC and BCG demonstrate efficacy in prolonging the time to recurrence with respect to the period of observation before treatment, so reducing the hospitalisation rate for TUR of the recurrent tumours, but no difference in the recurrence rates was observed between MMC and BCG as primary treatment[31]. The rationale for intravesical therapy is to maximize the exposure of tumors located in the bladder cavity to therapeutics agents while limiting the systemic exposure and thereby limiting the host toxicities; the primary goal is to eradicate existing or residual tumors through direct cytoablation or immunostimulation[32].

In a recent meta- analysis of 7 trials, sylvester and co workers demonstrated a 39% reduction in the risk of recurrence when a single dose of cytotoxic chemotherapy (epirubicin in 3 trials, Mitomycicn-C in 2 trials , thiotepa in one trial ,and pirarubicin in 1 trial) was delivered post operatively after TURBT compared with TURBT alone[13]. Solsona and colleagues performed randomized controlled trial of mitomycin C versus no treatment in patients with single ,primary or recurrent, non muscle invasive tumors The beneficial effect of a single instillation in the prevention of tumor cell implantation were mainly noted during the first 12 months[32]. One immediate instillation reduces the recurrence rate, not only in low risk patients with single tumors but also in patients with multiple tumors for whom one instillation is an incomplete treatment[13].

One immediate instillation after TUR reduces the recurrence rate and is recommended in all patients with papillary tumors except in the case of a perforated bladder or extended TUR (grade A). In patients at low risk of recurrence, no further treatment is recommended prior to recurrence[33]. Long-term prophylaxis with MMC results in a significantly reduced recurrence rate in intermediate-/high-risk bladder cancer with a comparable toxicity profile in comparison to short-term MMC or short-term BCG. Our study showed no significant decrease of the recurrence rate in low-risk tumors with six adjuvant MMC instillations. This treatment approach thus does not represent an alternative to early instillation[34].

My study also showed that one immediate intravesical instillation of chemotherapy significantly decreases the risk of recurrence after TUR in patients with stage Ta T1 single and multiple bladder cancer. It is the treatment of choice in patients with a single, low risk papillary tumor and is recommended as the initial treatment after TUR in patients with higher risk tumors.

CONCLUSIONS

One perioperative (within 6 hours of TURBT) intravesical instillation of chemotherapy significantly decreases the risk of recurrence after TURBT in patients with stage Ta T1, single and multiple papillary bladder cancer in low risk as well as high risk tumors. One immediate instillation after TUR reduces the recurrence rate and is recommended in all patients with papillary tumors .In patients at low risk of recurrence, no further treatment is recommended prior to recurrence.

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