

Adjuvant Treatment of Intermediate Risk Non-muscle Invasive Bladder Cancer

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ABSTRACT: Despite continuous improvement of diagnosis, surgical and adjuvant treatment procedures for non-muscle invasive bladder cancer (NMIBC), their natural development is still influenced by the high rates of tumor recurrence and progression. The study aims at assessing the value of adjuvant intravesical chemotherapy within the therapeutic protocol for operated intermediate risk non-muscle invasive bladder cancers. We analyzed recurrence and progression rates for patients within two samples: group A included 76 patients with intermediate risk NMIBC treated by transurethral resection (TUR) alone between 1995 and 1999 and group B included 89 patients with the same diagnosis with 8 – 12 Farmorubicin 50 mg intravesical instillations associated with the initial TUR between 2000 and 2004. For group A we recorded a 3 months recurrence rate of 27.6% and a general recurrence rate of 38.1% at one year and 51.3% at three years. The recurrence rate was lower for group B at 3 months (14.6%) as well as significantly lower ($p < 0.05$) at one (23.6%) and three years (34.8%). Most NMIBC recurrences were recorded within one year of follow-up (75%), more than 50% of them being present at the first cystoscopy (3 months). Progression rate was insignificantly 3% lower for group B, probably due to incomplete pathology data.

KEYWORDS: non-muscle invasive bladder cancer, recurrence, progression

Introduction

Bladder cancer (BC) is the most common tumor of the urinary tract and second among all uro-genital tumors after prostate cancer [1].

With an overall incidence of 5% of all new annually diagnosed cases of cancer, bladder cancer is fourth most common tumor in men, after prostate, lung and colon cancer [2].

In terms of pathology, bladder cancer is divided by the T element, in non-invasive bladder cancer (Tis, Ta) and invasive bladder cancer (T1-T4). A series of clinical, prognosis and especially therapeutic criteria, led to their separation in two currently accepted groups: **non-muscle invasive bladder cancer** (Tis, Ta, T1-NMIBC) and **muscle invasive and metastatic bladder cancer** (T2-T4) [3].

Despite the continuous improvement of diagnostic techniques, operative and complementary therapeutic protocols addressing NMIBC, their natural evolution remains marked by high rates of recurrence (up to 80%) and tumor progression (about 15%) [4].

Although non-invasive bladder tumors share the same conservative surgical treatment (Transurethral resection - TUR) they are still a very heterogeneous group in terms of prognosis with different values of recurrence, progression or death risk, depending on their clinical and histopathological characteristics. Considering the high risk of tumor recurrence and/or progression following TUR, actual guidelines

recommend intravesical chemotherapy within 6 hours after resection for all NMIBC [5].

These tumors were divided based on clinical and evolutive criteria by the European Organization for Research and Treatment of Cancer (EORTC) into three different risk categories and benefit from different adjuvant treatment strategies as recommended by the European Association of Urology (EAU) [5]:

- low risk NMIBC: pTa G1 – single, <3 cm, TaG1/G2 non-recurrent;
- intermediate risk NMIBC: TaG3, unique, T1G1/G2, TaG1/G2, multifocal or recurrent;
- high risk NMIBC: pT1 recurrent, multifocal, pT1G3, Ta/T1 > 3 cm, CIS.

According to risk group recommendations after TUR are: simple follow-up for the low-risk group, adjuvant intravesical chemotherapy for the intermediate-risk group and adjuvant intravesical immunotherapy with BCG vaccine for the high risk group.

Objective

The study aims to evaluate the benefit of implementing intravesical chemotherapy in the complementary treatment protocol for intermediate risk non-muscle invasive bladder cancers.

Patients and method

Between 1995 and 1999, 243 new patients with bladder cancer (average incidence of 48.6 new cases/year) were registered and 68% had

NMIBC (167 cases). According to the EORTC classification, 86 patients were classified as intermediate risk NMIBC (51% of total). Treatment included TUR followed by intravesical chemotherapy with 50 mg *Farmorubicin* for 10 patients while for the other 76 patients TUR only was performed so that this group was selected for the study as group A (control group).

Similarly between 2000 and 2004 we recorded a total of 297 new cases of bladder cancer, 212 NMIBC (71%) and 97 patients with intermediate risk (45%). Treatment included TUR followed by intravesical chemotherapy with 50 mg *Farmorubicin* for 89 patients that were included in group B (study group) while 8 patients were treated by TUR only. The study includes the analysis of tumor recurrence rates of the two groups of patients:

- **Group A:** 76 patients with intermediate risk NMIBC treated with TUR only between 1995 and 1999;

- **Group B:** 89 patients with the same diagnosis who underwent TUR associated with 8 to 12 sessions intravesical instillation of 50 mg *Farmorubicin* between 2000 and 2004.

Patients were followed by quarterly cystoscopy (\pm TUR if recurrence was diagnosed) in the first two years and biannual cystoscopy in the third year. Follow-up period ranged from 24-48 months (mean 29.6 months).

Data was statistically analyzed using MS Excel and MedCalc software, evaluating tumor recurrence rate, odds ratio and recurrence free survival using Kaplan-Meier curves.

Results

There were a total of 75 cases of tumor recurrence for group A and 58 for group B, with a mean of 1.92 and 1.75 recurrences/patient respectively. Single tumor recurrence was diagnosed for 8 patients in group A (20.5%) and 10 in group B (32.2%) while the rest had two (17 in group A - 43.5% and 14 in group B - 45.1%) or more recurrences (14 in group A - 35.9% and 7 in group B - 22.6%). One patient in group A had a total of 7 recurrences/36 month follow-up. At the first cystoscopy control (3 months) we registered a recurrence rate of 27.6% for group A and 14.6% for group B (54% and 42% of all recurrences in the two groups respectively).

Most NMIBC recurrences (89%) occurred in the first year of follow-up in both groups: 38.1% recurrence rate for group A and 23.6% recurrence rate for group B (74.3% of all recurrences in group A and 67.7% in group B). At three years the total recurrence rate was 51.3% (39 cases) for group A and 34.8% (31 cases) for group B (Table 1, Fig.1).

Table 1. NMIBC recurrence rates for the two patient groups (ns = not significant)

NMIBC Recurrence	Group A (n=) %		Group B (n=) %		p =
3 Months	21	27.6%	13	14.6%	ns
12 Months	29	38.1%	21	23.6%	< 0.05
36 Months	39	51.3%	31	34.8%	< 0.01

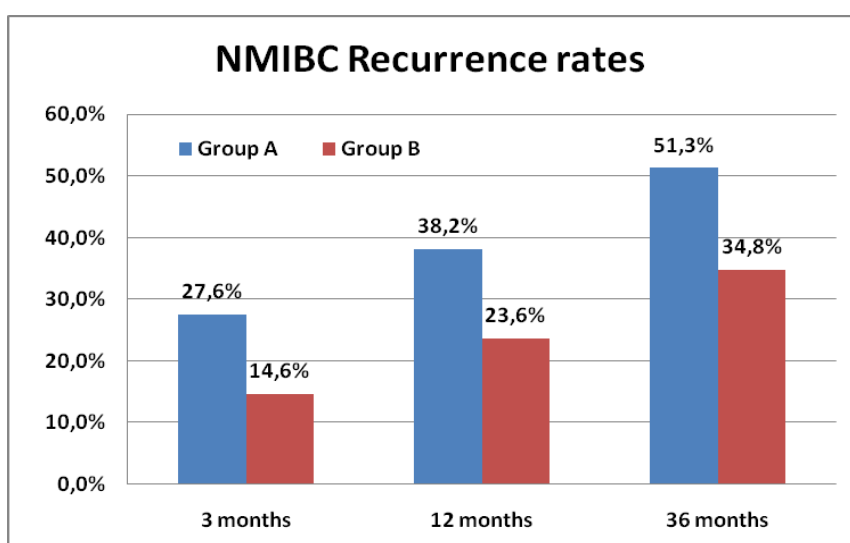


Fig.1. Recurrence rates in the two groups

We further analyzed the recurrence free survival rates for the two groups using Kaplan-Meier curves (Fig. 2, 3).

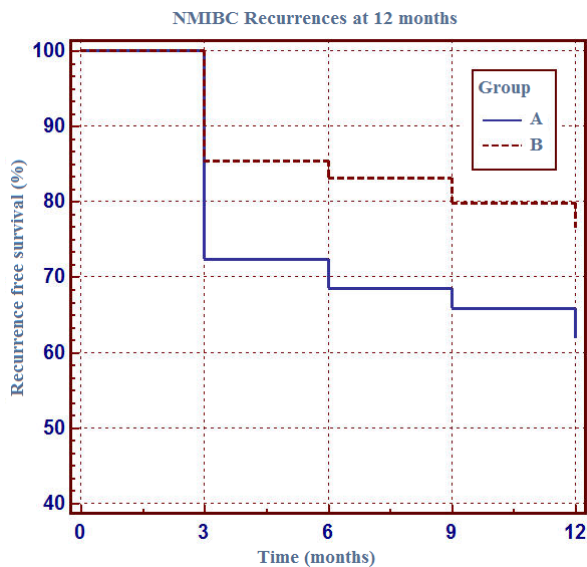


Fig.2. Recurrence free survival after one year of follow-up for the two groups, Kaplan-Meier analysis ($p < 0.05$, OR = 1.71, 95% CI = 1.03 to 3.47).

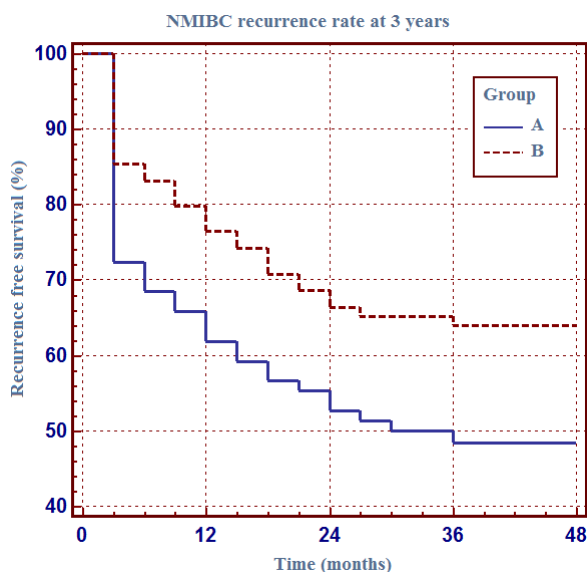


Fig.3. Recurrence free survival after 3 years of follow-up for the two groups, Kaplan-Meier analysis ($p < 0.05$, OR = 1.591, 95% CI = 1.03 to 2.80).

A significant difference was noticed as early as 3 months (over 85% recurrence free survival for group B compared to 72% for group A) and maintained statistical significance ($p = 0.0368$) throughout the follow-up period (even after 3 years). The relative risk (RR) for a patient without adjuvant treatment (group A) to develop tumor recurrence was 1.7150 (95% CI = 1.0337 to 3.4665) at one year follow-up and 1.5909 (95% CI = 1.0331 to 2.8024) for the follow-up period of 36 months.

NMIBC progression rates could not be precisely determined due to lack of complete pathological evaluations of all recurrences.

In group A, from 58 patients with complete pathological evaluations (76.3%), 21 had recurrences during this period and 7 of them (12%) had tumor progression, 5 with grade progression G (8.6%) and 2 with tumor depth progression T (3.4%).

In group B progressions were recorded for 6 patients (9%), 3 with tumor depth progression T (4.5%) and 3 with grade progression G (4.5%) of the total 67 patients with complete data histopathology (75.2%).

Discussion

Similar to our study, medical literature shows that most NMIBC recurrences occur in the first year of follow-up (75%) with a significant recurrence rate of over 50% at the first follow-up cystoscopy[5].

The statistically significant benefit of the adjuvant treatment ($p < 0.05$) was proved by the reduction of recurrence rates in group B (Table 2) by 10.3% at 3 months of follow-up (OR = 0.4480; 95%CI = 0.2066 – 0.9713), 12% at one year (OR = 0.5005; 95%CI = 0.337 – 0.869) and 16.5% at 3 years (OR = 0.5071; 95%CI = 0.2710 – 0.9487). Adjuvant intravesical chemotherapy treatment becomes thus a significant independent positive prognosis factor.

For progression rates we recorded a non-significant 3% difference between the two groups probably due to insufficient recurrence pathology evaluation results

Tabel 2. The benefit of the adjuvant treatment in group B

NMIBC (Group B vs. Group A)	Benefit	OR (95%CI)	p =
Recurrence rate at 3 Months	10.3 %	0.4480 (0.2066 - 0.9713)	< 0.05
Recurrence rate at 12 Months	12.0 %	0.5005 (0.2552 - 0.9816)	< 0.05
Recurrence rate at 36 Months	16.5 %	0.5071 (0.2710 - 0.9487)	< 0.01
Progression rate at 36 Months	3.1 %	0.729 (0.2150 – 1.6731)	ns

The recurrence rates in our study (for group B) are similar with those in the recent literature where they vary between 15% and 25% at 3 months [6], 25 – 30 % at one year and 35 – 40 % or more at 3 to 5 years[7]. Recurrence rates are 5 – 10% lower if immediate postoperative bladder chemotherapy is used as recommended by EAU guidelines [8,9].

Conclusions

Adequate administration of postoperative adjuvant intravesical chemotherapy in patients with intermediate risk non-muscle invasive bladder cancer is a positive prognosis factor as it leads to a significant (10 – 16 %) recurrence rate reduction in the first 3 years of follow-up.

Due to a still elevated recurrence rate at 3 months (23-38%) it is necessary to commonly use one immediate postoperative bladder chemotherapy instillation for all patients with operated NMIBC as recommended by EAU guidelines.

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