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UROLOGY – ORIGINAL PAPER

# T1G3 high-risk NMIBC (non-muscle invasive bladder cancer): conservative treatment versus immediate cystectomy

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**Abstract**
*Background* The management of stage T1 poorly differentiated G3 bladder cancer invading the lamina propria continues to be debated. These tumours are associated with a high risk of recurrence and progression; concomitant carcinoma in situ and/or multifocality are negative prognostic factors. Choosing between a preserving approach such as transurethral resection of the bladder (TURB) followed by maintenance bacillus Calmette-Guerin (BCG) and an invasive approach like cystectomy is critical.
*Patients and methods* Overall, 80 patients underwent TURB and RE-TURB followed by intra-vesical induction treatment with BCG plus maintenance (Group A) while 72 patients underwent immediate radical cystectomy with extended lymphadenectomy (Group B). Patients were divided into 3 subgroups: uni-focal tumours, multi-focal tumours and carcinoma in situ associated lesions. In Group A, time to first recurrence and time to progression were analysed. A comparison was made between Group A and Group B regarding progression-free survival, cancer-specific survival and overall survival with a median follow-up time of 8.3 years.
*Results* As far as concerns Group A patients, 42 recurrences (52.5%) were reported in a median time of 10.4 months (range 3–26) and 25 progressions (31.2%) in a median time of 25 months (range 3–68). As far as concerns time to first recurrence and time to progression, both the Kaplan–Meier survival curves obtained are significant and *P* values are, respectively, 0.0263 and 0.0011. Comparing Groups A and B patients, 25 progressions (31.2%) in a median time of 25 months (range 3–68) and 18 progressions (25%) in a median time of 25.9 months (range 4–72), respectively, were recorded. Regarding overall survival, at 10 years, 24 deaths (42.5%) occurred in a median time of 55.4 months (range 12–94) in Group A and 42 deaths (58.3%) in a median time of 54.9 months (10–100) in Group B. Cancer-specific survival was evaluated in Group A with a total of 18 deaths (22.5%) in a median time of 47.5 months (range 16–78), and in Group B with a total of 16 deaths (22.2%) in a median time of 45.7 months (range 16–88). The progression-free survival Kaplan–Meier curve is not significant, the *P* value being 0.3801; the overall survival curve is significant with a *P* value of 0.0487 while the cancer-specific survival curve is not significant with a *P* value of 0.9762.
*Discussion* In Group A, considering "time to first recurrence", the difference is greater between unifocal lesions and multifocal or Cis-associated lesions. Conversely, for "time to progression", there is a greater difference between unifocal and multifocal tumours and Cis-associated tumours. Looking at

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"progression-free survival" in Group A and Group B patients, there is no statistically significant difference, like in cancer-specific survival. A statistically significant difference was observed in overall survival being in favour of conservative treatment thus reflecting that conservative treatment is not burdened by all the surgical and post-operative complications of cystectomy.

*Conclusions* Although NMIBC invading the lamina propria, stage G3, with or without Cis-associated lesions are burdened both by a high volume of recurrences and progressions, cystectomy could be considered an aggressive approach. New biological markers are now needed which are able to predict the behaviour of the cancer and to guide the decision-making process between conservative or aggressive treatment.

**Keywords** Bladder cancer · NMIBC · BCG · Cystectomy

## Introduction

Management of stage T1 poorly differentiated G3 bladder cancer, invading the lamina propria, continues to be a matter of debate, bladder tumours involving the lamina propria have a significantly worse prognosis than those confined to the mucosa (Ta) [1]. Today, these tumours are defined as non-muscle invasive bladder cancer and account for approximately 75% of all bladder tumours, and of these, 20–25% invade the lamina propria (stage T1) [2]. Category T1 transitional cell carcinoma (TCC) of the bladder wall is associated with a high risk of recurrence and progression; concomitant carcinoma in situ (Cis) and/or multifocality are negative prognostic factors for recurrence and progression [3]. Cis is a high-grade non-invasive malignant tumour, the characteristic of which is the tendency to rapid progression; moreover, diagnosis is difficult and is achieved by the combination of abnormal cytology and cystoscopy with biopsies. These tumours are labelled as high-risk non-muscle invasive bladder cancers (NMIBC). The multifocal, with or without Cis, T1 high-grade papillary urothelial carcinoma is associated with a recurrence rate of 62–78% and a progression rate of 17–45% [4]. Choosing between a less invasive approach such as TURB (trans-urethral resection), followed by BCG induction plus maintenance, and an invasive approach such as cystectomy is critical.

Many experts consider proposing immediate cystectomy as reasonable, despite the well-known complications, for those with NMI cancer with multiple recurrent high-grade tumours, high-grade T1 tumours, and high-grade tumours with concomitant Cis; moreover, cystectomy is advocated in patients with BCG failure non-muscle invasive cancer. Delaying cystectomy, in these patients, may lead to a decrease in disease-specific survival [5]. Nevertheless, radical cystectomy (RC) is affected by a high rate of peri-operative mortality and morbidity, and the patient's quality of life (QoL) is definitely involved.

At present, no randomized clinical phase III trials on early cystectomy versus the preserving approach (TURB + bacillus Calmette-Guerin (BCG)) in the management of non-invasive BCa, exist. Comparing trans-urethral resection plus intra-vesical BCG therapy with other conservative forms of treatment, a significant difference can be found in terms of recurrence rates and progression [6, 7].

For Cis treatment, BCG (induction + maintenance) is the gold standard. BCG would appear to prevent and delay progression to muscle invasive disease. BCG refractory patients are at high risk of progression and cancer death, and cystectomy is, therefore, the treatment of choice [8]. Although BCG is burdened by more severe side-effects compared with chemotherapy, it has demonstrated to result in a longer time to recurrence and less risk of progression. In the treatment of high-risk NMIBC, the various adjuvant therapy options are BCG plus interferon alpha, new chemotherapy agents (gemcitabin) and device-assisted instillation (Synergo or photodynamic therapy). These treatment options must be considered experimental on account of the limited data available. The search for new drugs, for use in adjuvant endovesical treatment, is now necessary on account of the many BCG-related side-effects.

In this retrospective, non-randomised, single institution trial, an analysis was made of 80 patients with high-risk non-muscle invasive tumours treated with trans-urethral resection of the bladder (TURB) followed by adjuvant intra-vesical treatment with

BCG (6 weekly instillations as induction and 36 months treatment with 3 weekly instillations as maintenance) while 72 patients were submitted to immediate cystectomy. In the present study, we evaluated the time to first recurrence and time to progression in the TURB + BCG group and compared findings between the two groups concerning cancer-specific survival, overall survival and progression-free survival.

## Patients and methods

Between January 1995 and January 2001, 152 patients, mean age 70 years (range 36–80), with a male/female ratio 110/42 (72.4%/27.6%), all suffering from high-risk non-muscle invasive bladder cancer at first diagnosis, were selected to evaluate the efficacy of an organ preserving approach with trans-urethral resection of the bladder followed by adjuvant immuno-therapy with BCG or an immediate radical cystectomy. Exclusion criteria were as follows: recurrent tumour, stage T2 or higher neoplasm, performance status 3–4 (ECOG) [9], age > 80 years; based on these criteria 22 patients were excluded. Before any treatment option, a signed consent form was obtained from each patient, and all patients were informed, with all the details, regarding the therapeutic choice for the particular disease, moreover, all patients were requested to provide a detailed surgical and medical history.

In accordance with these criteria 80 patients were selected who underwent TURB and RE-TURB followed by intra-vesical induction treatment with BCG, plus maintenance (Group A) and 72 patients who underwent immediate radical cystectomy (RC) with extended lymphadenectomy (Group B). Patient characteristics are outlined in Tables 1 and 2.

In Group A, a treatment scheme was adopted based on TURB followed, after 4 weeks, by a further TURB (RE-TURB) with resection of the primary tumour site and collection of biopsy specimens from the suspect areas; muscle tissue was present in all samples. Overall, 14 patients were excluded as there was no evidence of muscularis propria in the histological specimen. The use of a second resection offers the advantage of more accurate staging, as well as less risk of downstaging of the disease and, furthermore, resection of eventually undetected lesions is possible. Four weeks after the second TURB, adjuvant immunotherapy was started with BCG, Connaught substrain (Immucyst®), using a treatment programme of instillation 1 weekly, for 6 weeks, followed by 3 years of maintenance instillation with 3 weekly instillation every 3 or 6 months. In the event of disease progression, in this group, a deferred RC was performed. Patients in the conservative approach arm were divided into 3 subgroups according to tumour characteristics; of the 80 patients in Group A, 21 (26.2%) presented T1G3 unifocal tumour, 33 (41.2%) T1G3 multifocal tumour and 26 (32.5%) T1G3 + Cis tumour. Patients in Group B were also divided into 19 (26.4%) unifocal tumours, 30 (41.6%) multifocal tumours and 23 (32%) T1G3 + Cis tumours. In Group A and B, the treatment was based on a TURB followed by a RE-TURB and, finally, patients were submitted to immediate RC within 60 days of the endoscopic treatment, in order to ensure accurate staging of the disease. All patients in Group A received a median number of 5 TURB (range 1–9), unlike Group B that underwent only TURB and second look TURB. Follow-up for those patients who underwent TURB + BCG consisted of cystoscopy and urinary cytology, in 3 samples, every 3 months for the first 2 years and, thereafter, every 6 months; abdomino-pelvic computerized tomography (CT) and excretory urography were performed every 2 years. Follow-up for patients who underwent immediate radical cystectomy consisted of chest X-ray, abdomino-pelvic ultrasound and haemato-chemical tests every 3 months for the first 2 years and, thereafter, every 6 months; abdomino-pelvic CT and urinary cytology every 6 months for the first 2 years and, thereafter, every 12 months; total body bone scan and excretory urography were carried out every 2 years [10].

All anatomical specimens were submitted to 'Department of Pathology, Sapienza University of Rome'.

In Group A, time to the first recurrence and the time to progression were analysed. BCa recurrences are defined as histologically proven bladder cancer after initial trans-urethral resection; progression is defined as muscular invasion (stage T2 or higher) or metastatic disease (M+) [3].

A comparison was made between Group A and Group B regarding progression-free survival, cancer-specific survival and overall survival (with a median

**Table 1** Group A patients characteristics (TURB + BCG)

| TURB + BCG (80 patients) | T1G3 unifocal | T1G3 multifocal | T1G3 + Cis | *P* |
|---|---|---|---|---|
| *n* (%) | 21 (26.2%) | 33 (41.2%) | 26 (33.5%) | |
| *Age n (%)* | | | | |
| ≤60 | 4 (19%) | 10 (30.3%) | 4 (15.4%) | NS |
| 60–70 | 11 (52.4%) | 15 (45.5%) | 12 (46.1%) | |
| 70–80 | 6 (28.6%) | 8 (24.3%) | 10 (38.5%) | |
| Median | 70.6 | 70.5 | 70 | |
| *Gender n (%)* | | | | |
| M | 15 (71.4%) | 25 (75.8%) | 20 (77%) | NS |
| F | 6 (28.6%) | 8 (24.2%) | 6 (23%) | |
| *Performance status (ECOG) n (%)* | | | | |
| 0 | 15 (71.4%) | 27 (81.8%) | 20 (76.9%) | NS |
| 1 | 5 (23.8%) | 4 (12.2%) | 5 (19.3%) | |
| 2 | 1 (4.8%) | 2 (6%) | 1 (3.8%) | |
| *Tumour size n (%)*[a] | | | | |
| ≤1 cm | 11 (52.4%) | 15 (45.5%) | 8 (30.8%) | NS |
| >1 cm ≤ 3 cm | 10 (47.6%) | 18 (54.5%) | 15 (57.6%) | |
| ≥3 cm | 0 (0%) | 0 (0%) | 3 (11.5%) | |
| Median | 1.5 | 1.5 | 2 | |
| Recurrence rate *n* (%) | 6 (28.6%) | 19 (57.6%) | 17 (65.4%) | 0.0263 |
| Progression rate *n* (%) | 2 (9.5%) | 9 (27.3%) | 14 (53.8%) | 0.0011 |

*NS* Not significant

[a] Maximum size of largest tumour resected

follow-up time of 8.3 years). Progression-free survival is defined as any histologically proven or clinical progression of the disease including demonstration of metastases; cancer-specific survival is the interval from the operation to death from the disease while overall survival refers to the interval from the operation to death from any reason, including cancer and all other causes.

Estimates of survival probability were calculated using the Kaplan–Meier method. Differences in survival, between the various patient subgroups, were assessed using the log-rank test indicating the standard errors for the probability of survival based on Greenwood's formula.

Statistical evaluations were performed using 5 separate analyses for the outcomes of time to first recurrence, time to progression, overall survival, cancer-specific survival and progression-free survival. Survival time was calculated from the time of restaging TUR. All parameters were estimated using the Kaplan–Meier survival curve method and compared with the long-rank test. Moreover, cancer-specific survival was estimated with the cumulative incidence function, considering death from other and unknown causes as a competing risk, and was compared using a modified $X^2$ test. Also used was the MedCalc complete statistical programme latest version 11.4.4, released November 23, 2010 (Mariakerke, Belgium). *P* values were calculated using Pearson's chi-square test and were considered significant with a $P < 0.05$.

## Results

Outcomes of this trial have been divided into two classes: Group A findings and results obtained from the comparison of both groups. A total of 80 patients treated with an organ preserving approach (TURB followed by a RE-TURB and then by endovesical instillation with induction + maintenance BCG) were divided into: 21 T1G3 unifocal tumours, 33 T1G3 multifocal tumours and 26 T1G3 + Cis tumours. Patients with unifocal lesions presented 6

**Table 2** Group B patients' characteristics (radical cystectomy)

| Cystectomy (72 patients) | T1G3 unifocal | T1G3 multifocal | T1G3 + Cis | *P* |
|---|---|---|---|---|
| *n (%)* | 19 (26.4%) | 30 (41.6%) | 23 (32%) | |
| *Age n (%)* | | | | |
| ≤60 | 4 (21%) | 8 (26.7%) | 7 (30.4%) | NS |
| 60–70 | 10 (52.6%) | 18 (60%) | 10 (43.5%) | |
| 70–80 | 5 (26.3%) | 4 (13.3%) | 6 (26.1%) | |
| Median | 69.4 | 69.4 | 69.9 | |
| *Gender n (%)* | | | | |
| M | 12 (63.3%) | 20 (66.7%) | 17 (74%) | NS |
| F | 7 (36.8%) | 10 (33.3%) | 6 (26%) | |
| *Performance status (ECOG) n (%)* | | | | |
| 0 | 14 (73.7%) | 21 (70%) | 15 (65.2%) | NS |
| 1 | 4 (21%) | 6 (20%) | 8 (34.8%) | |
| 2 | 1 (5.3%) | 3 (10%) | 0 (0%) | |
| *Tumour size n (%)*[a] | | | | |
| ≤1 cm | 7 (36.8%) | 9 (30%) | 5 (21.7%) | NS |
| >1 cm ≤ 3 cm | 9 (47.4%) | 18 (60%) | 15 (65.2%) | |
| ≥3 cm | 3 (15.8%) | 3 (10%) | 3 (13.1%) | |
| Median | 1.5 | 2 | 1.5 | |
| *Stage n (%)* | | | | |
| pT1 | 16 (84.2%) | 22 (73.3%) | 15 (65.2%) | NS |
| pT2 | 3 (15.8%) | 7 (23.3%) | 6 (26%) | |
| pT3 | 0 (0%) | 1 (2%) | 2 (8.7%) | |
| *Lymph node n (%)* | | | | |
| + | 0 (0%) | 3 (10%) | 1 (4.4%) | NS |
| − | 19 (100%) | 27 (90%) | 22 (95.6%) | |

*NS* Not significant

[a] Maximum size of largest tumour resected

recurrences in a median time of 14 months (range 7–22), patients with multifocal lesions, 19 in a median time of 10.6 months (range 3–26) and patients with Cis-associated lesions, a total of 17 recurrences in a median time of 8.9 months (range 3–24). Considering these three subgroups together, a total of 42 first reccurrences (52.5%) were found in a median time of 10.4 months (range 3–26).

The 'time to first recurrence' Kaplan–Meier survival curve obtained is significant, with a *P* value of 0.0263 and chi-square of 7.2782 (Fig. 1).

As far as concerning tumour progression, 2 progressions were observed with a median time of 52.5 months (range 45–60) in T1G3 unifocal patients, 9 with a median time of 33.2 months (range 6–68) in T1G3 multifocal patients and 14 with a median time of 15.7 months (range 3–54) in T1G3 + Cis patients. Regarding patients presenting progression, a total of 25 (31.2%) with disease progression were observed in a median time of 25 months (range 3–68). Of the 25 patients that progressed 20 (25%) had an organ-confined disease with a median progression time of 26.7 months (range 3–68) and 5 (6.2%) had distant metastases with a median progression time of 18.2 months (range 6–45). The 20 patients not presenting metastases underwent radical deferred cystectomy while the 5 patients with metastases were not eligible for deferred cystectomy.

The "time to progression" Kaplan–Meier survival curve is significant with a *P* value of 0.0011 and chi-square of 13.6923 (Fig. 2).

Radical aggressive treatment with early cystectomy was performed in 72 patients with non-muscle

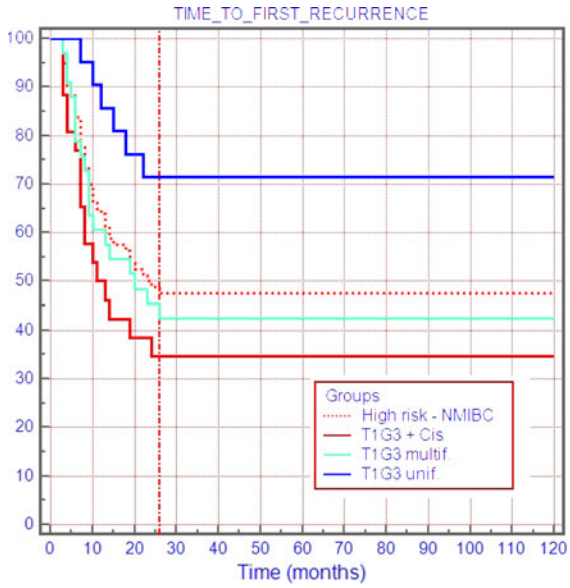


**Fig. 1** Conservative treatment (TURB + BCG); time to first recurrence. Total number of patients (High risk—NMIBC): 80, T1G3 unifocal: 21, T1G3 multifocal: 33, T1G3 + Cis: 26. On *vertical dotted line* number of patients in percent, on *horizontal dotted line* time in months

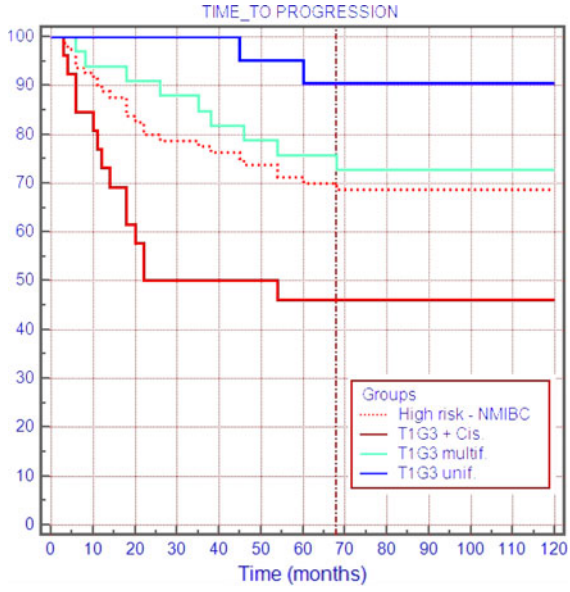


**Fig. 2** Conservative treatment (TURB + BCG); time to progression. Total number of patients (High risk—NMIBC): 80, T1G3 unifocal: 21, T1G3 multifocal: 33, T1G3 + Cis: 26. On *vertical dotted line* number of patients in percent, on *horizontal dotted line* time in months

invasive tumours with T1G3 multifocal lesions or T1G3 with Cis-associated lesions; 19 were solitary T1G3, 30 multiple T1G3 and 23 T1G3 + Cis. The pathological evaluation following the main surgery revealed that 53 patients (73.6%) had pT1 tumours, 16 (22.2%) had a stage pT2 tumour and 3 (4.2%) a pT3 tumour, or higher. By means of the lymph node pathological evaluation, 4 patients (5.5%) were found to have lymphatic metastases.

Comparing all the 72 patients (Group B) submitted to radical cystectomy with the Group A patients submitted to TURB + BCG 3 Kaplan–Meier survival curves were obtained: progression-free survival, overall survival and cancer-specific survival.

With regard to progression-free survival, we had 25 progressions (31.2%) with a median time of 25 months (range 3–68), in the conservative arm, and 18 cases of progression (25%) with a median time of 25.9 months (range 4–72) in the cystectomy arm. Considering all the patients, a total of 43 progressions (28.3%) were observed, with a median time of 25.4 months (range 3–72).

Regarding overall survival at 10 years, 34 patients (42.5%) died within a median time of 55.3 months (range 12–94) in Group A and 42 patients (58.3%) died within a median time of 54.9 months (range 10–100) in Group B. Overall survival, referring to all 152 patients, was calculated taking into consideration a total of 76 deaths (50%), in a median time of 55.1 months (range 10–100).

Cancer-specific survival was evaluated in Group A with a total of 18 deaths (22.5%) in a median time of 47.5 months (range 16–78) and in Group B with a total of 16 deaths (22.2%) in a median time of 45.7 months (range 16–88). Considering Group A and Group B together, there were 34 (22.4%) deaths with a median time of 46.6 months (range 16–88).

The Kaplan–Meier progression-free survival curve is not significant with a $P$ value of 0.3801 and chi-square of 0.7704 (Fig. 3); the overall survival curve is only slightly significant with a $P$ value of 0.0487 and chi-square of 3.8873 (Fig. 4); the cancer-specific survival curve is not significant with a $P$ value of 0.9762 and chi-square of 0.0008880 (Fig. 5).

## Discussion

High-grade (G3) bladder cancer at stage T1, with or without associated Cis, is characterised by a large number of recurrences and progressions, representing

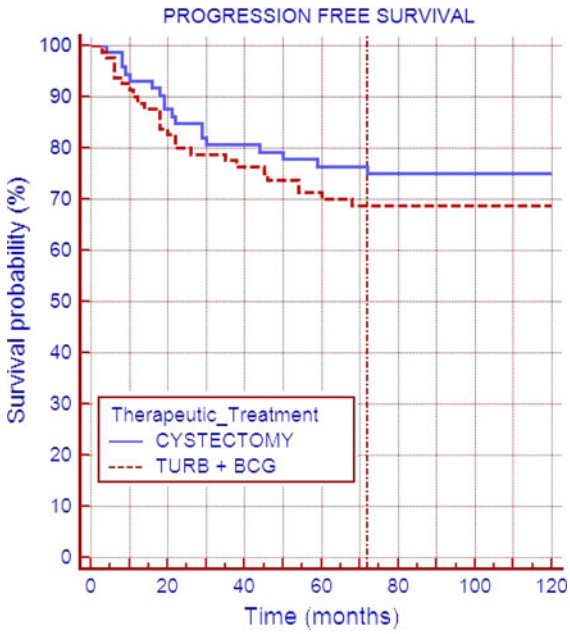


**Fig. 3** Conservative treatment (TURB + BCG) versus aggressive treatment (cystectomy); progression-free survival. Total number of patients (High risk—NMIBC): 152, TURB + BCG: 80, Cystectomy: 72. On *vertical dotted line* number of patients in percent, on *horizontal dotted line* time in months

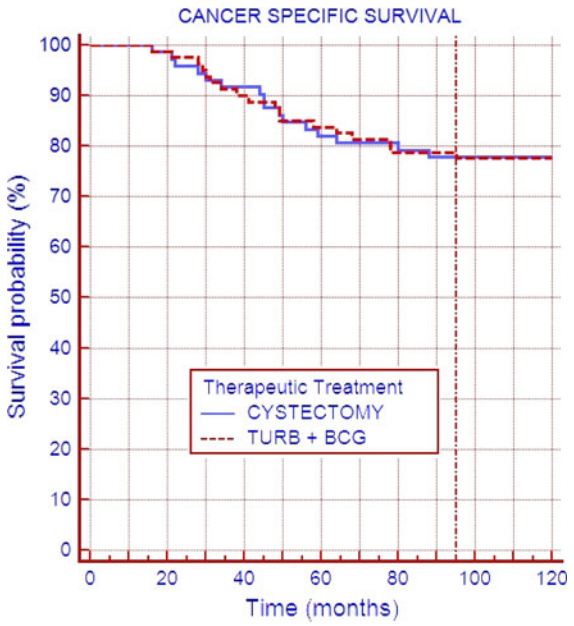


**Fig. 5** Conservative treatment (TURB + BCG) versus aggressive treatment (cystectomy); cancer-specific survival. Total number of patients (High risk—NMIBC): 152, TURB + BCG: 80, Cystectomy: 72. On *vertical dotted line* number of patients in percent, on *horizontal dotted line* time in months

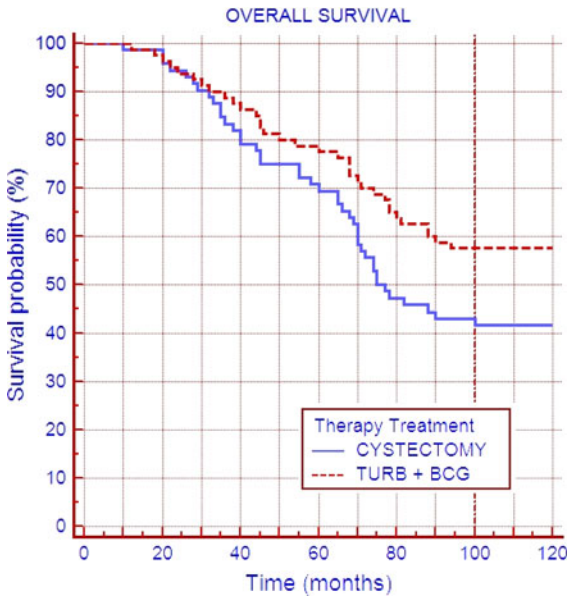


**Fig. 4** Conservative treatment (TURB + BCG) versus aggressive treatment (cystectomy); overall survival. Total number of patients (High risk—NMIBC): 152, TURB + BCG: 80, Cystectomy: 72. On *vertical dotted line* number of patients in percent, on *horizontal dotted line* time in months

approximately 20–30% of non-muscle invasive bladder tumours [11]. The present retrospective, non-randomized study analyses the differences in terms of recurrence and progression in patients submitted to a conservative approach, TURB and RE-TURB followed by endovesical BCG, Connaught strain, instillation (induction + maintenance for up to 3 years). Moreover, a comparison was made between patients submitted to a conservative approach and patients submitted to a radical cystectomy, a non-conservative approach. The second review is focused on progression-free survival time, cancer-specific survival time and overall survival time.

For ethical reasons, randomisation between these two treatment modes was not feasible as we are discussing completely different options and which are burdened by a completely different quality of life, side-effects, follow-up and psychological impact. As these two options are both considered effective for bladder cancer, at this stage and grade [12], the decision-making process, between the aggressive and conservative treatment, was delegated to the patient, each of whom, after an exhaustive explanation

regarding all the therapeutic aspects, advantages and side-effects related to each approach, was asked to decide. Thereafter, the patient was asked to sign a consent form related to the proposed treatment.

A total of 80 patients underwent conservative treatment and were divided into unifocal tumours, multifocal tumours and Cis-associated tumours, all presenting invasion of the lamina propria (T1).

The Kaplan–Meier charts clearly indicate a significant difference in first recurrence time between these three categories, moreover, it is important to emphasize the different rates in the 3 groups. This is clearly evident as there is a considerable difference between unifocal lesions and multifocal or Cis-associated lesions which have a similar recurrence rate and time. Considering progression time, the difference is clearly significant and, in this case, a major difference was observed between unifocal and multifocal tumours and tumours with Cis, both in terms of rate and time. Despite the fact that all patients were submittetd to TURB, followed by a second look and by BCG adjuvant therapy (induction + maintenance), together with a strict follow-up, which is considered the gold-standard treatment scheme, a large number of recurrences and progression to a muscle invasive cancer were observed. The recurrence rate was estimated at 52.5% in a median time of 10.4 months while the progression rate was 31.2% in a median time of 25 months. Considering these two parameters, it can be seen that as far as concerns recurrence, the focality of the tumour is more important, while for progression, Cis always plays a fundamental role as already demonstrated in several studies. BCG adjuvant therapy is of primary importance since, as described in several studies, it has the capability to reduce not only recurrence but also progression rate compared to TUR alone. Shelley et al. [13] reported, for intermediate and high-risk TCC, in six randomised trials focusiong on 585 patients (more than 50% stage T1), a recurrence rate of 26% with BCG and 51% with TUR alone. In a meta-analysis, by Bohle et al. [14] involving 2,798 patients, the difference is also underlined in recurrence rate between immunotherapy with BCG and chemotherapy with MMC, 38.6% of recurrences versus 46.4%, respectively. Another interesting trial regarding BCG following trans-uretheral resection compared with mitomycin C adjuvant therapy reports, respectively: a disease-free survival rate of 35% versus 48% for Ta/T1 tumours and 33% versus 54% for patients with Cis-associated (follow-up 39 months) [15]. Sylvester et al., performed a meta-analysis of 4,863 patients, with a median follow-up of 2.5 years, treated, respectively, with TUR + BCG or with a different option consisting in TUR alone or TUR + chemotherapy or TUR + different immunotherapy. In the two groups, there is a difference in the progression rate of 9.8% versus 13.8%, in favour of the BCG scheme. In the meta-analysis, the different progression rate between papillary tumours and Cis tumours is emphasized, which was reported to be, respectively, 6.4 and 13.9% and the importance is stressed of maintenance therapy to obtain advantages in the progression rate [6]. In an EORTC phase III trial (number 30906), 168 patients were randomised to receive BCG (84) or epirubicin (84) and the overall CR rate was 56% for epirubicin and 65% for BCG, time to bladder tumour recurrence, after CR, was longer in patients treated with BCG vs those receiving epirubicin [16]. Bohle et al. [17] reported, in a meta-analysis of 2,410 patients, the better results with maintenance BCG versus mitomycin C as far as concerns progression rate. It should be pointed out, however, that this study is not homogeneous for high-risk non-muscle invasive tumours. BCG adjuvant therapy is more efficacious when it is applied with a scheme that includes induction followed by 3 years of maintenance, as demonstrated in a SWOG trial by Lamm et al. [18] in which a significant difference is evident in terms of recurrence-free survival and in terms of progression-free survival. Bearing in mind the toxicity is remarkable as mytomic C and alternative adjuvant treatments have fewer systemic and local side-effects than BCG, this would mean, in high-risk TCC, that MMC should be considered an alternative choice for patients intolerant to BCG who refuse cystectomy [14]. In a study on 487 patients submitted, after trans-urethral resection, to BCG (induction followed by 3 years' maintenance), 20.3% of the patients withdrew from treatment due to side-effects; 14.8% on account of local side-effects and 9.4% for systemic side-effects [19].

Even if RC could be an "overtreatment" for many patients because bladder-sparing surgery, followed by intravesical adjuvant therapy, is effective in more than 50% of patients [20], these data would appear to suggest that TURB followed by maintenance BCG could be inadequate in this heterogeneous group of

TCC patients and that cystectomy could represent an appropriate treatment option to minimize recurrences and progressions. Although RC is indicated, in many cases, it is characterized by a large number of deaths related partly to cancer and partly to mortality and morbidity due to operative and post-operative complications.

The second part of the present retrospective trial is, in fact, focused on a comparison between 152 patients with high-risk non-muscle invasive BCa treated, respectively, with TURB + BCG (80 patients) and with radical cystectomy (72 patients). Considering the three main comparison tools, namely, progression-free survival, overall survival and cancer-specific survival, there are clearly differences between the two subgroups.

Looking at progression-free survival, it is clear that there is a slight difference in terms of progression rate and progression-free survival time in favour of radical cystectomy that, however, is not statistically significant. This difference may be interpreted with the major radicality of RC, compared with TURB + BCG, and with the possibility of down-staging that occurs with conservative treatment. Down-staging is a common problem that can, in part, be solved by a trans-urethral resection that always includes muscular tissue and secondly by RE-TURB performed 4 weeks after the first resection. Dalbagni et al. [21] reported 13% under-staging in patients treated with TURB followed by RE-TURB. Moreover, during cystectomy an extended lymphadenectomy is always performed and, in many cystectomy series, there are up to 6% of T1 tumours with lymph node metastases [22]. We performed cystectomy in Group B patients and the pathological evaluation confirmed that 19 patients (26.4%) had a TCC, stage pT2 or higher, and that 4 patients (5.5%) also had lymph node involvement. This result underlines the critical point of downstaging and the importance of always performing an extended lymphadenectomy and this confirms that often conservative treatment may be inadequate for the approach to apparent non-muscle invasive bladder cancer.

Overall survival, in groups A and B, is the only parameter that is statistically significant. We noted, in fact, 58.3% of deaths in Group B and 42.5% in Group A. This result reflects that conservative treatment is not burdened by all the operative and post-operative complications of cystectomy. Stein et al., in a study involving 1,054 patients submitted to radical cystectomy with lymphadenectomy described, 2.5% of peri-operative deaths with 28% of early complications [23]. Patients submitted to cystectomy report changes in sexual, gastro-intestinal and genito-urinary habits [9]. Furthermore, it is important to mention the changes in Qol (quality of life) retrieved by patients submitted to RC. Kulkarni et al. [24] reported, in a comparison between cystectomy and TURB followed by BCG, that the aggressive approach is more suitable for younger and otherwise healthy patients, instead of conservative treatment that is more suitable for older patients with comorbidities.

The third parameter analysed is cancer-specific survival for which we found no statistical differences between groups A and B. Looking at the Kaplan–Meier curves and the statistical data, it is clearly evident that there are no differences between two subgroups, the curves are stacking and the percentages of the cancer-specific survival rate are almost the same, 22.5 and 22.2%, respectively. This parameter is very important since it shows that both the approaches to high-risk non-muscle invasive bladder cancer are effective and are characterized by the same results, in terms of survival. Even if cystectomy is more radical and offers a more definitive chance for cure, we observed the same results with TURB followed by adjuvant intra-vesical instillation of BCG (Connaught strain). These results, confirmed by the same outcomes, further demonstrate that both approaches are suitable but that it is also important to point out that to obtain this result it is fundamental after TURB, to perform a RE-TURB within 4 weeks and to start BCG induction treatment after 4 weeks and, thereafter, to prescribe maintenance BCG for 3 years. Moreover, close follow-up is extremely important, to be conducted, in a first analysis, by cystoscopy and cytology, initially every 3 months and, thereafter, after 6 months.

At present, the treatment of choice for Bca at high-risk of recurrence and progression, still remains to be established. The critical point is that some tumours might be selected which could be well controlled by conservative treatment, while other tumours need radical cystectomy, for better control and a better life expectancy. In this regard, it should not be forgotten that outcomes may differ in patients treated with deferred cystectomy instead of early cystectomy [25]. There is a vital need to better understand the natural

history of the disorder and to establish parameters able to predict the evolution of the pathological condition. This is important in order to immediately select those patients that need early cystectomy rather than patients not requiring an aggressive approach. At present, the cancer is evaluated only by means of clinical criteria and by histo-pathological differentiation. The parameters usually considered are as follows: tumour stage (differentiation in T1a, T1b, T1c), tumour grade, histotype, Cis-associated, multifocality and number of tumours, tumour size, prostatic urethra involvement and recurrence rate. EORTC risk tables offer a practical tool with which to estimate the probability of recurrence and progression in patients with stage Ta T1 bladder cancer [4]. This is, however, still not sufficient and the only feasible means would be molecular differentiation of the cancer.

Molecular biology can provide better information on the aggressiveness and natural history of BCa and also the possibility of recurrence and progression to an invasive muscle disease or metastases. At present, no biomolecular marker can be defined as the best. Many markers such as survivin, bax [26], bcl-2 [26], Ki-67, and galectin-3 [27] have been studied, but at present none can be considered the perfect marker able to predict the course of the disease. Another important and promising prognostic factor is the evaluation of circulating tumour cells (CTC) that have also been found in non-muscle invasive bladder cancer. We have also performed a preliminary study on 54 patients with T1G3 TCC in which CTC were evaluated in a blood sample withdrawn before transurethral resection of the tumour. The results are very promising since circulating cells were found in 44% of patients and 92% of these patients were survivin positive [28]. Clearly, this is the ideal way to obtain better characterization of this neoplasm.

## Conclusions

Although non-muscle invasive bladder cancer penetrating the lamina propria, stage G3, with or without associated Cis is burdened by frequent recurrences and progressions, cystectomy could be considered a too aggressive approach. Cancer-specific survival for the two treatment option is clearly comparable, whereas, overall survival, for which there is a statistical significant advantage, is in favour of conservative treatment. However, the question still remains open: which patients should be considered the best candidates for conservative management and which would be the best for radical cystectomy? Which patients give rise to the problem of choice between the two treatment options [29]?

There is now an urgent need for new biological markers able to predict the behaviour of the cancer and to guide the decision-making process between conservative treatment (TURB and RE-TURB followed by adjuvant endovesical therapy with BCG) and an aggressive approach (radical cystectomy with extended lymphadenectomy).

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