

Survival after primary and deferred cystectomy for stage T1 transitional cell carcinoma of the bladder

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Abstract

Context: The optimal time of cystectomy for nonmuscle invasive bladder cancer (NMIBC) is controversial.

Aim: This study aims at comparing cancer-specific survival in primary versus deferred cystectomy for T1 bladder cancer.

Settings and Design: Between 1990 and 2004, a retrospective cohort of 204 patients was studied.

Materials and Methods: Primary cystectomy at the diagnosis of NMIBC was performed in 134 patients (group 1) and deferred cystectomy was done after failed conservative treatment in 70 (group 2) Both groups were compared regarding patient and tumor characteristics and cancer-specific survival.

Statistical Analysis Used: Cancer-specific survival was calculated using the Kaplan-Meier method.

Results: Mean follow-up was 79 and 66 months, respectively, in the two groups. Tumor multiplicity was more frequent in group 2; otherwise, both groups were comparable in all characteristics. The definitive stage was T1 in all patients. Although the 3-year (84% in group 1 vs. 79% in group 2), 5-year (78% vs. 71%) and 10-year (69% vs. 64%) cancer-specific survival rates were lower in the deferred cystectomy group, the difference was not statistically significant. In group 2, survival was significantly lower in cases undergoing more than three transurethral resections of bladder tumors (TURBT) than in cases with fewer TURBTs.

Conclusions: Cancer-specific survival is statistically comparable for primary and deferred cystectomy in T1 bladder cancer, although there is a non-significant difference in favor of primary cystectomy. In the deferred cystectomy group, the number of TURBTs beyond three is associated with lower survival. Conservative treatment should be adopted for most cases in this category.

Key Words: Cystectomy, deferred, non-muscle invasive bladder cancer, primary

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INTRODUCTION

Non-muscle invasive bladder cancer (NMIBC) accounts for 75% of bladder transitional cell carcinomas (TCCs). This

category includes Ta, T1 and Tis [carcinoma *in situ* (CIS)] according to the TNM classification.^[1] The two main problems of NMIBC are recurrence and progression.

Approximately 25% of Ta tumors, the majority of T1 tumors (more than 50%), and all CIS are high-grade lesions.^[1] According to risk categorization, there are two subgroups, namely, the low-risk (single, small, low-grade, Ta tumor without CIS) and high-risk tumors (Ta or T1 high-grade tumors or CIS alone).^[2] The 5-year recurrence rate is 31% and 78% for the low-risk and high-risk tumors, respectively,^[2] whereas the 5-year progression rate is 0.8% and 45% for low- and high-risk tumors, respectively.^[2] In CIS, progression to muscle invasion occurs in 40-83% of the cases.^[3]

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The high-grade non-muscle invasive TCC leads to death from cancer in 10-40% of cases and thus calls for an aggressive management philosophy.^[4] It has been argued that T1G3 bladder cancer should not be classified as “superficial” bladder cancer since it is not confined to the urothelial surface and it is a highly malignant tumor with a variable and unpredictable biologic potential.^[5] In addition, the pathologic staging at the time of cystectomy for patients considered for primary cystectomy indicates that 35-50% harbor muscle invasive disease, including micrometastases in 10-15%.^[6]

Treatment with intravesical bacillus Calmette-Guerin (BCG) reduces both the risk of recurrence and the risk of progression and is the treatment of choice in high-risk papillary tumors and in patients with CIS.^[7] On the other hand, radical cystectomy remains the gold standard for patients with muscle invasive urothelial carcinoma of the bladder and is an important option for patients with high-grade non-muscle invasive disease who have recurrent or progressive disease after intravesical therapy.^[7]

The timing of cystectomy for high-risk NMIBC is a matter of considerable debate.^[6,8-10] Some investigators have advocated primary radical cystectomy once the diagnosis of high-risk disease is made,^[6,8,9] while others have criticized primary radical cystectomy.^[10]

What will happen if cystectomy is done immediately after failure of BCG therapy in this subgroup of patients? Will the survival be different from that in a homologous group undergoing primary cystectomy? This retrospective study was carried out in order to answer this question by comparing the cancer-specific survival in primary versus deferred cystectomy in a retrospective cohort having NMIBC.

MATERIALS AND METHODS

This study was performed between March 1990 and July 2004 and included 204 patients (184 males and 20 females) of a median age of 55 years (range 29-79). Primary cystectomy at the time of diagnosis of NMIBC (based mainly on multiplicity of the tumor) was carried out in 134 patients (group 1; median age 54 years; 118 males). Deferred cystectomy was conducted in 70 patients (group 2; median age 55 years; 66 males). Deferred cystectomy was defined as cystectomy within one month of failure of one or two consecutive 6-week courses of intravesical BCG or other intravesical therapy. The time between the first transurethral resection of bladder tumor (TURBT) and cystectomy and the number of TURBTs were determined in group 2.

Patients were excluded from the study if they had muscle invasive disease after failure of the intravesical therapy. Cases that died from unrelated illness were not included in this study.

Before cystectomy, the patients were evaluated every three months during the first two years and every six months thereafter.^[11] Clinical examination was performed regularly to detect evidence of disease recurrence and/or progression. Symptoms and signs of relevant complications and side effects of intravesical therapy were noted. Evaluation at each visit included urinalysis, urine culture, serum creatinine, complete blood count, abdominal ultrasonography, cysto-urethroscopy and urine cytology. Excretory urography or magnetic resonance urography (MRU) was performed annually. Liver function tests and chest X-ray were done when necessary.

After cystectomy, the patients were oncologically and functionally evaluated every three months during year one and every six months thereafter.

Oncological evaluation included physical and bimanual examination to detect any abnormalities in the cystectomy bed, most importantly, local recurrence. Also, abdominal ultrasound was done in all cases. Unless otherwise indicated, computerized tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis was performed every year to exclude oncologic recurrence and/or metastasis. If there was a suspicious finding on physical examination or ultrasound, further evaluation was done by CT or MRI. Panendoscopy was conducted if there was bleeding via the urethra or hematuria. Bone scintigraphy was requested if the patient complained of persistent bone aches. Upper tract imaging by excretory urography or magnetic resonance urography (MRU) was conducted annually unless otherwise indicated.

Both groups were compared regarding patient and tumor characteristics, morbidity after cystectomy, follow-up, bladder cancer-specific survival, mode of diversion and pattern of recurrence and metastasis after cystectomy. In the deferred cystectomy group, the time between the first TURBT and cystectomy (within 2 vs. more than 2 years) and number of TURBTs were correlated to cancer-specific survival.

Cancer-specific survival was calculated using the Kaplan-Meier method and the results were compared using the Log Rank test. Significance was set at a value of $P < 0.05$.

The study proposal and design were approved by the local committee.

RESULTS

Mean follow-up (range) was 79 (6-181) and 66 (6-190) months, respectively, in the two groups ($P = 0.19$). Apart from tumor multiplicity, which was more frequent in group 2, both groups were comparable regarding other patient and tumor

characteristics [Table 1]. The definitive stage was T1 in all patients, while the grade was G1, G2, and G3 in 19 (9.3%), 157 (77%) and 28 (13.7%) patients, respectively [Table 2]. Again both groups were comparable regarding the mode of diversion after cystectomy, lymph node status, postoperative morbidity and sites of local recurrence or distant metastasis [Table 2].

Although the 3-year, 5-year and 10-year cancer-specific survival rates were lower in the deferred cystectomy group, the difference was not statistically significant [Figure 1, Table 3]. The survival rates were 78% versus 71% at 5 years (Log Rank $P=0.25$).

In the deferred cystectomy group, the time between the first TURBT and cystectomy (within 2 vs. more than 2 years) did not affect the cancer-specific survival except for the actuarial

10-year survival rate, which was lower for cystectomies performed more than 2 years than for earlier cystectomies [Figure 2, Table 4].

On the other hand, cancer-specific survival was significantly lower in cases undergoing more than three TURBTs than with

Table 1: Patient and tumor characteristics in primary and deferred cystectomy groups

Parameter	Primary cystectomy group 1 (%)	Deferred cystectomy group 2 (%)	Total number of patients (%)	P value
Number of patients	134 (65.7)	70 (34.3)	204	
Median age in years/range	54/31-79	55/29-71	55/29-79	
Sex (Male/Female)	118/16	66/4	184/20	0.16
Site of tumor				0.02
Anterior wall	7 (5.2)	6 (8.6)	13 (6.4)	
Posterior wall	35 (26.1)	13 (18.6)	48 (23.5)	
Left lateral wall	15 (11.2)	6 (8.6)	21 (10.3)	
Right lateral wall	12 (9)	2 (2.9)	14 (6.9)	
Multicentric	56 (41.8)	38 (54.3)	94 (46)	
Domal	5 (3.7)	3 (4.3)	8 (3.9)	
Others	4 (3)	2 (2.9)	6 (2.9)	
Grade				0.42
G1	12 (9)	7 (10)	19 (9.3)	
G2	108 (80.6)	49 (70)	157 (77)	
G3	14 (10.4)	14 (20)	28 (13.7)	
Carcinoma <i>in situ</i> (CIS)	36 (26.9)	22 (31.4)	58 (28.4)	0.27

Table 2: Operative and postoperative parameters in primary and deferred cystectomy groups

Parameter	Primary cystectomy group 1 (%)	Deferred cystectomy group 2 (%)	P value
Lymph node status			0.16
Positive	2 (1.5)	4 (5.7)	
Negative	132 (98.5)	66 (94.3)	
Diversion			0.55
Rectal bladder	1 (0.7)	0	
Ileal-conduit	61 (45.5)	25 (35.7)	
Urethral Kock pouch with valve	12 (9)	6 (8.6)	
Cutaneous Kock bladder	8 (6)	5 (9)	
Modified rectal double folded rectosigmoid	5 (3.7)	1 (1.4)	
Ileal W-neobladder	36 (26.9)	31 (44.3)	
Others	3 (2.2)	0	
Morbidity			0.53
Wound sepsis	2 (1.5)	1 (1.4)	
Adhesive ileus	2 (1.5)	0	
DVT	2 (1.5)	1 (1.4)	
Urinary leakage	0	1 (1.4)	
Others	2 (1.5)	1 (1.4)	
Site of local recurrence			0.41
Urethral	7 (5.2)	3 (4.3)	
Pelvic	8 (6)	4 (5.7)	
Site of distant metastasis			0.09
Bone	1 (0.7)	3 (4.3)	
Liver	3 (2.2)	1 (1.4)	
Lung	6 (4.5)	0	
Nodal	1 (0.7)	0	
Multiple	4 (3)	1 (1.4)	
Others	0	1 (1.4)	

DVT: Deep vein thrombosis

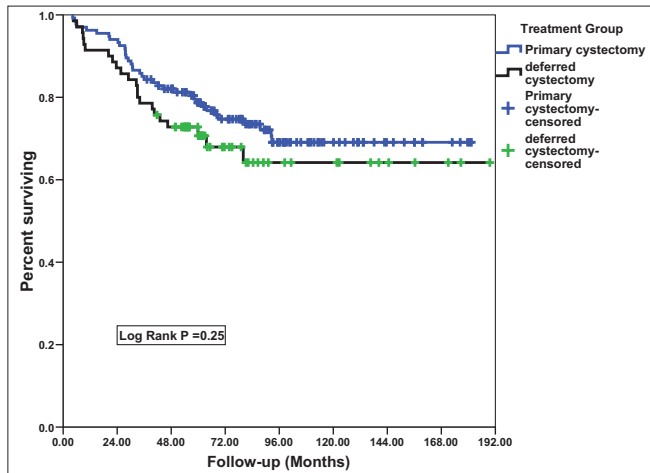


Figure 1: Cancer-specific survival after primary and deferred cystectomy for T1 bladder TCC

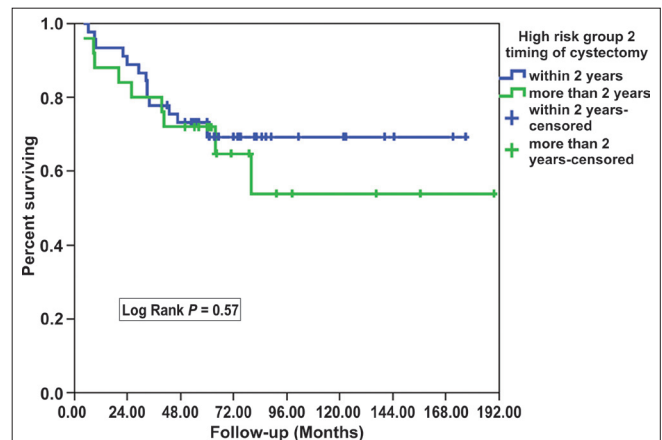


Figure 2: Cancer-specific survival correlated to the time of cystectomy in the deferred cystectomy group

Table 3: Cancer-specific survival in the primary and deferred cystectomy groups

Group	3-year % ± SE	5-year % ± SE	Actuarial 10-year % ± SE
Primary cystectomy	84 ± 3	78 ± 3	69 ± 5
Deferred cystectomy	79 ± 5	71 ± 6	64 ± 6

Log Rank $P = 0.25$. SE: Standard error of survival

fewer TURBTs in the deferred cystectomy group [Figure 3, Table 4].

DISCUSSION

Although demonstration of a survival advantage for primary cystectomy in NMIBC in the current study is expected and supported by other investigators, yet the statistically insignificant difference is not expected. Primary cystectomy has been shown in previous retrospective studies to have a survival benefit.^[6,8,12]

Volkmer *et al.* showed that primary T1G3 bladder TCC treated by primary cystectomy had a survival benefit over recurrent T1G3 treated by deferred cystectomy ($P=0.007$).^[12] Similarly, Stockle and coworkers reported a higher survival rate with primary cystectomy.^[8] In their study on T1 disease, the 5-year recurrence-free survival rate in the immediate cystectomy group was 90% compared with 62% in the deferred group.

Denzinger *et al.* in a study of 105 patients compared the long-term outcome in patients with initial T1G3 bladder cancer treated with primary versus deferred cystectomy for recurrent T1G3 or muscle-invasive bladder cancer after an initial bladder-sparing approach.^[9] They found that the 10-year cancer-specific survival rate was 78% in primary cystectomy and 51% in deferred cystectomy ($P<0.01$). They concluded that high-risk T1G3 tumors with two or more risk factors, that is, multifocal and/or >3 cm in size and/or with concomitant CIS, should be counseled about undergoing primary cystectomy, whereas a smaller and solitary initial T1G3 bladder cancer without CIS may be regarded for an organ-sparing approach. This conclusion goes hand in hand with the result of the current study, that is, the discrepancy in survival between primary and deferred cystectomy has been more marked at 10 than at 5 years.

Herr and Sogani in a group of high-risk NMIBC stated a survival rate of 92% when the cystectomy was performed within two years of initial BCG therapy compared with 56% in patients who underwent cystectomy more than two years after initial BCG therapy.^[6] This finding is not in accordance with our results in the deferred cystectomy group.

A major limitation of all these retrospective studies is that they are holding an unfair comparison between a primary

Table 4: Cancer-specific survival rate correlated to the time from initial diagnosis and to the number of resections (TURBs) in the deferred cystectomy group

Parameter	3-year % ± SE	5-year % ± SE	Actuarial 10-year % ± SE
Time of cystectomy			Log Rank $P = 0.57$
Within 2 years from initial diagnosis	78 ± 6	69 ± 7	69 ± 7
More than 2 years from initial diagnosis	80 ± 8	72 ± 9	54 ± 13
Number of TURBs			Log Rank $P = 0.01$
1-3	82 ± 5	73 ± 6	69 ± 7
More than 3*	50 ± 2	33 ± 2	33 ± 2

*Small number of patients in this group. SE: Standard error of survival

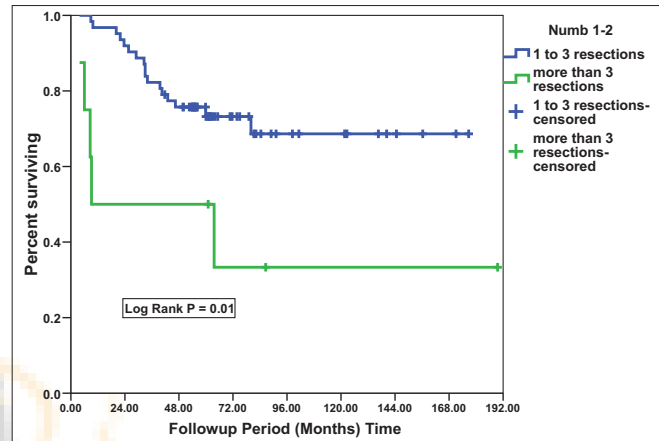


Figure 3: Cancer-specific survival correlated to the number of TURBs in the deferred cystectomy group

cystectomy for a pooled group of NMIBC with various risks for progression (good and bad cases) and another group of deferred cystectomy composed of only bad cases who failed conservative treatment. At the same time, the good cases that were successfully treated with conservative treatment were excluded in the deferred cystectomy group. In addition, some studies have included muscle invading tumors which were initially NMIBC in the deferred cystectomy group, a fact that will further jeopardize the fair comparison.

In the current study, the marginal insignificant difference in survival rates in the two groups of primary and deferred cystectomy can be explained by the fact that in all patients with deferred cystectomy we carried out the surgery within one month of BCG failure without considerable delay. In addition, the two groups of patients were comparable in stage and grade because we excluded cases that had developed muscle invasion after failure of conservative treatment.

The relation between the number of resections (TURBTs) and survival in the current study is new and needs to be supported by other trials.

A limitation to the present study is the low number of patients in the deferred cystectomy group and that it is retrospective. The optimal way to answer the question of the study is to do a prospective randomized trial comparing primary versus deferred cystectomy. However, such a study is difficult to conduct because it needs a long time and cystectomy will be unnecessarily conducted in a sector of patients undergoing primary cystectomy.

NMIBC staged as T1G3 presents a challenge to the urologists because the treatment of choice has not been defined to date.^[13] In some studies, high-risk NMIBC is defined as tumors with high grade and stage disease, tumors with CIS and those with chromosomal alterations.^[14] TURBT and adjuvant BCG therapy is accepted as the initial treatment for most patients with high-risk NMIBC.^[15] The results of the present study support this statement. However, the necessity to separate the NMIBC category into bad and good cases by clinical prognosticators or biomarkers seems to be of paramount importance.

The controversy lies on the definition of BCG failure and when to perform a radical cystectomy for tumors that recur without progression after BCG therapy. BCG failure has been defined as high-grade recurrence at three months of the first BCG course or after two courses.^[16] Some patients may benefit from a second course of BCG.^[17] This is because response rates of 36-83% have been reported with repeated courses of intravesical BCG after failure of an initial course or subsequent relapse.^[18]

However, patients with recurrent CIS who fail a second course of BCG have a very high risk of progression to muscle-invasive TCC.^[19] Additionally, relapses after two courses or more of BCG appear to be associated with poor outcomes, despite subsequent aggressive therapy.^[20] The conclusion of these trials as well as the current study is that cystectomy should be done immediately after failure of the second course of BCG.^[17,21-23] The model constructed by Kulkarni *et al.* about the most appropriate treatment for high-risk non-muscle invasive (stage T1; grade G3) bladder cancer demonstrated that younger patients with high-risk T1G3 bladder had a higher life expectancy (LE) and quality-adjusted life expectancy (QALE) with immediate cystectomy.^[24]

On the other hand, recent trials have demonstrated the potential benefits of therapies such as valrubicin, gemcitabine, interferon, and photodynamic therapy in salvaging BCG failures.^[25] In addition, although retrospective data suggest that deferred cystectomy for high-risk NMIBC TCC is associated with significantly worse survival,^[6,8,12] a recent survey suggests that many urologists are reluctant to consider cystectomy, even after two failed courses of intravesical therapy.^[26]

CONCLUSIONS

Cancer-specific survival has been proved to be statistically comparable for primary and deferred cystectomy in NMIBC, although a marginal non-significant difference in favor of primary cystectomy does exist. In the deferred cystectomy group, the time between first TURBT and cystectomy is not a significant factor affecting survival, except at 10 years. The number of TURBTs beyond three is associated with lower cancer-specific survival. The choice of diversion is not affected by deferred cystectomy. Conservative treatment should be adopted for most cases in this tumor category. However, the necessity to separate this tumor category into bad and good cases by clinical prognosticators or biomarkers is imperative.

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