



Bladder Cancer

Early Versus Deferred Cystectomy for Initial High-Risk pT1G3 Urothelial Carcinoma of the Bladder: Do Risk Factors Define Feasibility of Bladder-Sparing Approach?

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Abstract

Objectives: We compared long-term outcome in patients with initial pT1G3 bladder cancer (BC) treated with early versus deferred cystectomy (CX) for recurrent pT1G3 or muscle-invasive BC after an initial bladder-sparing approach. The aim of this study was to compare survival rates and to analyse the influence of the recognised risk factors multifocality, tumour size, and carcinoma in situ (CIS) in initial transurethral resection of the bladder.

Methods: Between 1995 and 2005, a total of 105 patients were diagnosed with initial pT1G3 BC featuring ≥ 2 risk factors. Forty-five percent had multiple tumours, 73% tumours > 3 cm in size, and 46% CIS. All patients were offered early CX. Fifty-one percent of patients opted for early and 49% underwent deferred CX for recurring BC. Risk factors were distributed evenly between the groups.

Results: Upstaging in the CX specimen was found in 30% of cases. No risk factor was related to upstaging. The 10-yr cancer-specific survival rate was 78% in early CX and 51% in deferred CX ($p < 0.01$). No risk factor predicted cancer-related death in early CX. In survival analysis, CIS was related to a lower cancer-specific survival rate in deferred CX ($p < 0.001$).

Conclusions: Early as opposed to deferred CX seems to prolong the cancer-specific survival rate in high-risk pT1G3 BC. Patients with CIS should be considered for early CX owing to reduced cancer-specific survival in case of deferred CX.

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1. Introduction

Urothelial cancer of the bladder (BC) staged as pT1G3 comprises roughly 10% of all non-muscle-invasive tumours [1]. Transurethral resection of the bladder (TURB) is the standard treatment for non-muscle-invasive BC. Despite often being referred to as superficial, pT1G3 BC features the histopathological, clinical, and biological characteristics of invasive tumours [2,3]. As opposed to truly superficial (ie, pTa disease), the treatment of choice for pT1G3 BC has not been defined to date. A secondary resection has been recommended in light of roughly 40% of residual disease in secondary TURB [4,5].

Organ-preserving approaches are successful in approximately 50% of all cases [6], and bacillus Calmette-Guérin (BCG) following TURB has been demonstrated to prolong the interval until recurrence, but not to improve overall survival [7]. However, the efficacy of an organ-preserving approach seems deficient in some cases because 30% of patients require deferred cystectomy (CX) and 30% ultimately die from metastatic disease [7].

Accordingly, early CX has been shown to improve tumour-specific survival rates [8]. Further support for an early aggressive approach is provided by understaging in the first TURB specimen in up to 50% of cases [9,10]. Despite low overall mortality after radical CX (<3%), most urologists prefer a less invasive approach and will resort to CX in recurrent and progressive cases only [11].

To date there has been no randomised clinical phase 3 trial comparing immediate CX with an organ-preserving approach. Various factors have been studied to distinguish between cases requiring early CX and those suitable for organ preservation. No biological markers have proved to be of sufficient prognostic value [12]. Sylvester et al [13] established a scoring system in pTa-1 disease with multifocal disease, concomitant CIS, and

tumour size >3 cm as factors predicting high-risk disease. He argued that the treatment of pT1G3 BC should be adapted to each tumour characteristic [13,14], but there are still conflicting reports on the predictive value of these factors [15]. Hurler et al [16] reported only tumour size and coexisting CIS to be correlated with outcome in 51 patients, and Lebret et al [17] found tumour size only, but not multifocality, to predict recurrence and progression in 35 patients. Brake et al [18] found no impact of concomitant CIS in 44 cases, and Pansadoro et al [19] could not establish any predictive value for the number of lesions or associated CIS in a series of 81 patients. To date, no study has been published on the relationship between these factors and clinical outcome in initial or deferred CX. In this analysis we compare the long-term results in patients with initial pT1G3 BC as diagnosed by TURB, and treated with either early CX or initially with an organ-preserving approach and CX upon disease recurrence of the same or muscle-invasive stages, with special regard to clinical risk factors in the initial TURB specimen.

2. Methods

2.1. Patients and treatment groups

The clinical and histopathological data of 189 consecutive initial BC staged as pT1G3 between 1995 and 2005 at our institution were reviewed. All cases were treated according to the EAU guidelines on bladder cancer [12]. To enter the analysis, patients had to present with a medical condition justifying major surgery and a combination (≥ 2 risk factors) of large tumours (>3 cm), multifocal disease, and/or concomitant CIS. Fifty-six percent ($n = 105$) of pT1G3 patients fulfilled the criteria, and all 105 patients entering the analysis were offered early CX accordingly. Of those high-risk patients, 51% ($n = 54$) opted for early CX on average 4 wk following the initial TURB. In contrast, 49% ($n = 51$) of patients had to undergo deferred CX owing to recurring BC. Table 1 provides detailed patient characteristics.

Table 1 – Characteristics of 105 patients after initial TURB undergoing early or deferred cystectomy (level of significance $p < 0.05$, not significant)

	Early CX	Deferred CX	p value
No. of patients	$n = 54$	$n = 51$	
No. of male patients	$n = 32$	$n = 30$	$p = 0.72$ (NS)
Median age (yr)	73.5 (range, 36–86)	75.2 (range, 43–84)	$p = 0.21$ (NS)
Multiple tumours $n = 47/105$ (45%)	$n = 23$	$n = 24$	$p = 0.24$ (NS)
Tumour size > 3 cm $n = 77/105$ (73%)	$n = 42$	$n = 35$	$p = 0.09$ (NS)
CIS $n = 48/105$ (46%)	$n = 21$	$n = 27$	$p = 0.18$ (NS)

CX, cystectomy; NS, not significant; CIS, carcinoma in situ.

Initially, all patients with deferred CX received 6 weekly intravesical BCG instillations invariably followed by a negative control TURB of the scar area and suspicious lesions 1–4 wk after the last instillation in all cases. Follow-up consisted of cystoscopy with bladder wash cytology every 3 mo, and the time interval between initial TURB and last follow-up was assessed. Patients underwent deferred CX for the first recurrence of pT1G3 (48%) and/or CIS (38%) or muscle-invasive disease (34%).

Median time from initial TURB to deferred CX was 11.2 mo (range, 3–19). One patient was found at 3 mo to have novel tumour staged as pT1 and graded as G3 by histopathology despite no finding in control TURB 6 wk after initial TURB. Accordingly, this case was interpreted as recurring BC. Upstaging was defined as muscle-invasive disease in the CX specimen to invasive stages (pT2–4) by histopathology despite the TURB specimen showing non-muscle-invasive BC.

2.2. Variation of tumour characteristics in treatment groups

Forty-five percent of all analysed patients had multiple tumours, 73% had tumours >3 cm in size, and 46% CIS. There was neither a significantly different distribution of tumour characteristics including involvement of the prostatic urethra between early CX and deferred CX nor a difference in age or gender (Table 1). Five percent and 7% of patients developed urothelial cancer of the upper urinary tract in early and deferred CX, respectively.

2.3. Statistical analysis

Complete follow-up information was available for all patients. Statistical analyses were completed with the use of SPSS, version 12.0 (SPSS Inc, Chicago, IL, USA). Contingency table analysis and two-sided Fisher's exact tests were used to study the statistical association between the two groups. Significant differences in cancer-specific survival were calculated by the Kaplan-Meier method, with significance evaluated by two-sided log-rank test. To determine cancer-related death, patients were reviewed at their last clinical follow-up appointment or the date of their death, related to the tumour. Deaths from causes other than BC were censored. Uni- and multivariate Cox proportional hazards models were applied to evaluate the relationship between cancer-specific survival, gender, tumour size, multifocality, CIS, and treatment group. *p* values <0.05 were considered significant.

3. Results

3.1. Patients

Mortality and morbidity of CX were low because 7% of patients had major surgical complications (fatal pulmonary embolism, *n* = 2; fatal cardiac ischaemia, *n* = 1; impaired wound healing, *n* = 4); complications were distributed equally between the treatment groups. Censored patients were followed for a

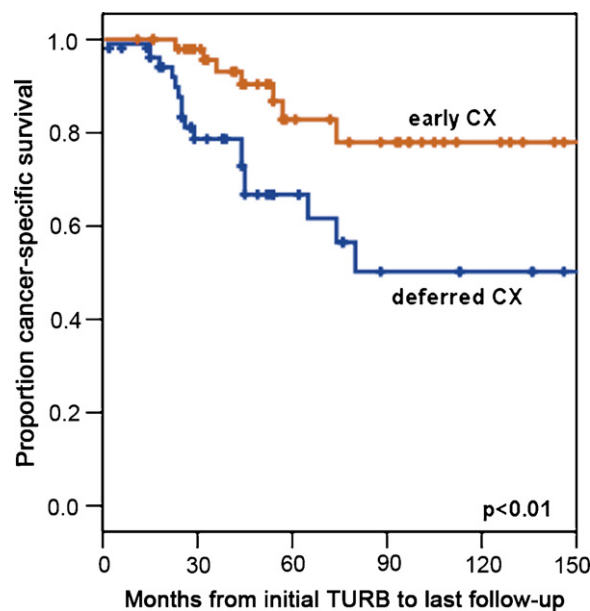


Fig. 1 – Kaplan-Meier analysis of cancer-specific survival in patients with early (orange line) versus deferred (blue line) cystectomy.

median of 5.4 yr (range, 0.9–12.1), and noncensored cases for a median of 5.1 yr (range, 0.4–12.5 yr), respectively. Upstaging after CX was found in 30% (*n* = 32) of all CX patients. There was no significant relationship between upstaging and treatment groups (early CX, *n* = 14; deferred CX, *n* = 18; *p* = 0.11).

Table 2 – Univariate Cox regression analysis of factors in relation to cancer-specific death in patients with pT1G3 BC

	Adjusted HR	95%CI	<i>p</i> value
Gender			
Male	1.00	(Reference)	
Female	0.63	0.13–1.79	0.95
Multifocality			
Multifocality	1.00	(Reference)	
No multifocality	1.69	0.93–4.30	0.23
Tumour size			
Tumour size >3 cm	1.00	(Reference)	
Tumour size <3 cm	2.03	0.87–3.71	0.20
CIS			
No CIS	1.00	(Reference)	
CIS	3.05	1.04–15.24	<0.001
Treatment group			
Early cystectomy	1.00	(Reference)	
Deferred cystectomy	5.11	2.14–18.66	<0.01

BC, bladder cancer; HR, hazard ratio; CI, confidence interval; CIS, carcinoma in situ.
Bold face represents *p* values <0.05.

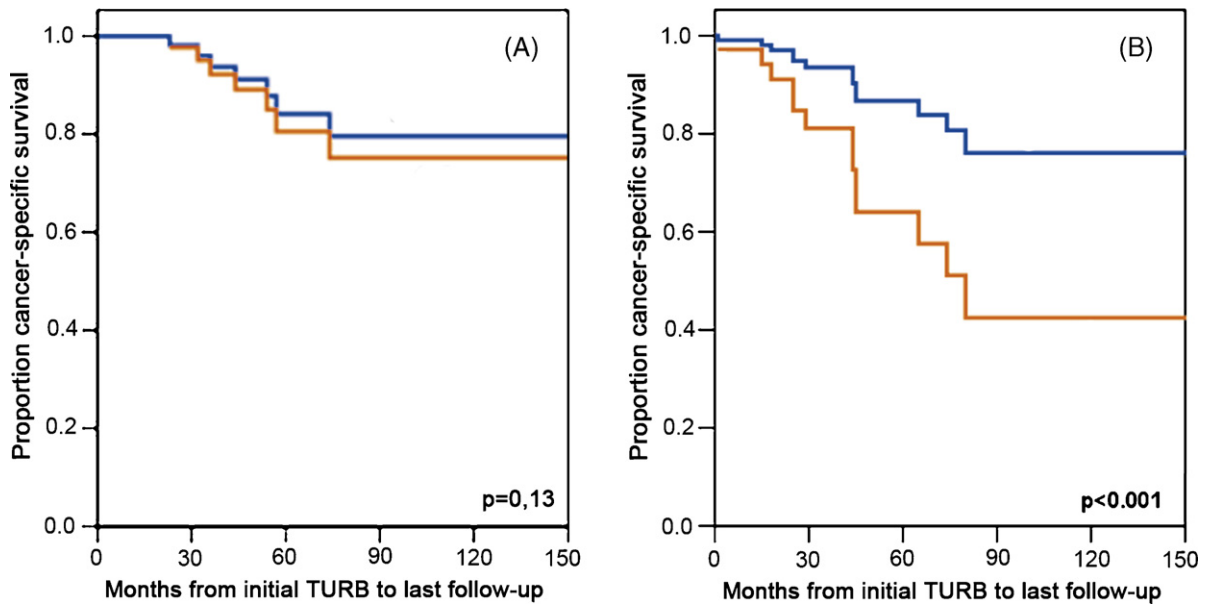


Fig. 2 – (A) Kaplan-Meier analysis of cancer-specific survival in patients undergoing early cystectomy with concomitant carcinoma in situ (CIS) (orange line) and without concomitant CIS (blue line). (B) Kaplan-Meier analysis of cancer-specific survival in patients undergoing deferred cystectomy with concomitant CIS (orange line) and without concomitant CIS (blue line).

3.2. Cancer-specific survival rate in relation to treatment mode

Early CX showed longer cancer-specific survival compared with deferred CX by log-rank test

($p < 0.01$). Eight percent of early CX cases and 24% of deferred CX cases died of progressive disease. Five- and 10-yr survival rates were 83% and 78% in the early CX group, and 67% and 51% in the deferred CX group, respectively (log-rank test, $p < 0.01$, Fig. 1).

Table 3 – Multivariate Cox regression analysis of factors in relation to cancer-specific death in patients with pT1G3 BC

	Step-wise reverse selection		
	Adjusted HR	95%CI	p value
Gender			
Male	1.00	(Reference)	
Female	0.79	0.15–1.73	0.23
Multifocality			
Multifocality	1.00	(Reference)	
No multifocality	2.19	1.27–6.69	0.12
Tumour size			
Tumour size >3 cm	1.00	(Reference)	
Tumour size <3 cm	1.72	0.40–3.56	0.43
CIS			
No CIS	1.00	(Reference)	
CIS	2.55	1.21–12.89	0.02
Treatment group			
Early cystectomy	1.00	(Reference)	
Deferred cystectomy	5.13	1.62–17.08	<0.01

BC, bladder cancer; HR, hazard ratio; CI, confidence interval; CIS, carcinoma in situ. Bold face represents p values <0.05.

3.3. Prediction of cancer-specific survival in univariate Cox regression analysis

Table 2 shows univariate Cox regression analysis of gender, multifocal tumours, tumours >3 cm in size, CIS, and treatment group in relation to cancer-specific survival. CIS (hazards ratio [HR], 3.05; 95% confidence interval [95%CI], 1.04–15.24; $p < 0.001$) and deferred CX (HR, 5.11; 95%CI, 2.14–18.66; $p < 0.01$) were found to be prognostic factors for cancer-specific death in univariate Cox regression analysis. CIS was significantly (log-rank test, $p < 0.001$) related to cancer-specific survival in deferred CX only (Fig. 2A and B).

3.4. Prediction of cancer-specific survival in multivariate Cox regression analysis

Table 3 shows deferred CX (HR, 5.13; 95%CI, 1.62–17.08; $p < 0.01$) to be the most significant factor predictive of cancer-related death, followed by CIS (HR, 2.55; 95%CI, 1.21–12.89; $p = 0.02$). Multifocal tumours, tumours >3 cm in size and gender were insignificant.

4. Discussion

Urothelial BC staged as pT1G3 presents urologists with a challenge because it has a poor outcome if treated like superficial (ie, pTa disease) [1,20]. The treatment of choice has not been defined to date. Early CX has been viewed as an overtreatment attributable to the quality of life as affected by urinary diversion. In 153 patients with pT1G3 disease, Shahin et al [7] found the disease never to recur in approximately 30% of cases and not to progress in 30% of recurring cases. Tumour progression to muscle-invasive cancer reduces the chance of survival dramatically [21].

According to Serrata et al [22], a bladder-sparing approach is an appropriate therapeutic option for initial management of selected pT1G3 BC. However, survival has been reported to be poor, even if pT1G3 BC is subjected to immediate radical surgery [23]. In 29 patients, Thalmann et al [6] reported a 5-yr tumour-specific survival rate of 69% in patients undergoing immediate CX.

Our larger series substantiates this view because the 10-yr tumour-specific survival rate was 78% in early CX. Thus, a relevant proportion of cases could not be cured of BC, despite CX for nominally non-muscle-invasive disease. However, because the 10-yr tumour-specific survival rate was 51% in deferred CX, early CX was associated with improved oncological outcome despite an even distribution of risk factors between the groups. It is furthermore notable that all high-risk pT1G3 BC patients reviewed at our institution who chose to undergo initial bladder-sparing approach, despite the offer of early CX, required delayed CX during follow-up, mainly owing to a first recurrence of pT1G3 BC. These findings support the notion that high-risk pT1G3 BC is an aggressive disease requiring timely radical surgery and make a point against bladder-sparing approaches. In contrast, a bladder-sparing approach can be attempted in conjunction with pT1G3 tumours without the risk factors mentioned.

Understaging of pT1G3 BC on the basis of TURB specimen is a confounding factor because cases taken for non-invasive BC and treated accordingly might be misjudged. Understaging in the initial TURB specimen is reported to occur in up to 50% of cases [9,10]. In our study, upstaging occurred in 30% of cases and was not correlated with any risk factors.

Although no such relation is described in the current literature either, all high-risk pT1G3 BC should be considered for a sufficiently deep control TURB because upstaging is a frequent event and

depth of invasion within the boundaries of the pT1 category has been described as a prognostic factor [2]. In the present series patients opting for early CX did not undergo control TURB, which probably contributes to the high rate of upstaged cases and calls for control TURB in all high-risk pT1G3 BC declining early CX. As the natural history of pT1G3 BC is uncertain and CX affects quality of life, most urologists are hesitant to pursue this procedure initially, and reserve it for recurrent and progressive BC [8,11].

Multiple tumours, CIS, and tumour size > 3 cm have been recognised as risk factors in non-muscle-invasive BC [13,14]. The value of risk factors in pT1G3 BC has been discussed [22]. However, current literature contains only sparse and conflicting data related to a bladder-sparing approach. Hurle et al [16] reported tumour size and coexisting CIS to be adverse factors. Brake et al [18] and Pansadoro et al [19] found no predictive value for the number of lesions or CIS in the TURB specimen.

Recently, Shariat et al [10] described the presence of concomitant CIS in organ-confined CX specimen to be an independent predictor of disease recurrence in remaining urethral mucosa. Although concomitant CIS was significantly related to lower tumour stages, it was not an independent predictor of cancer-specific mortality. Shariat et al inferred that the presence of concomitant CIS appeared to confer a worse prognosis in patients with non-muscle-invasive BC treated with radical CX. In accordance with these authors, concomitant CIS in early CX cases staged pT2 was not predictive of cancer-related death in our series.

Because no data have been reported to date on the relationship of these adverse characteristics in the initial TURB specimen and on tumour-specific survival in early versus deferred CX, our study presents the first such data to be published.

In contrast with Shariat et al's report [10] that concomitant CIS in organ-confined CX specimen has no influence on cancer-specific mortality, we found concomitant CIS in the initial TURB specimen to be predictive of cancer-related death in deferred CX. However, no adverse influence of any risk factor on cancer-specific survival was noted in early CX, underlining the feasibility of timely radical surgery in the presence of concomitant CIS in the initial TURB specimen.

There are no randomised studies comparing early CX with organ preservation and no prospective data allowing risk stratification for pT1G3 BC. However, our retrospective findings of improved

cancer-specific survival in early CX and adverse outcome in the presence of concomitant CIS in deferred CX should be considered in informing patients on treatment options for initial high-risk pT1G3 BC.

5. Conclusions

High-risk pT1G3 tumours 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 early CX, whereas a smaller and solitary initial pT1G3 BC without CIS may be regarded for an organ-sparing approach. CIS should be considered for timely radical surgery because it relates to reduced cancer-specific survival.

Conflicts of interest

The authors have nothing to disclose.

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