

A delay in radical cystectomy of >3 months is not associated with a worse clinical outcome

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OBJECTIVE

To examine the association between the interval from the last transurethral resection (TUR) to radical cystectomy (RC) and bladder cancer-specific outcome, as the decision to proceed to RC for an individual patient is complex, and recent reports suggest an interval from diagnosis to RC of >3 months is associated with adverse outcomes.

PATIENTS AND METHODS

The records of 592 patients who had RC were reviewed; the interval from the last TUR was analysed as both a continuous and categorical

variable (<3 vs ≥3 months). Logistic regression and survival analyses were used to evaluate the association between the interval to RC with pathological characteristics and clinical outcomes.

RESULTS

The mean (SD) actuarial cancer-specific survival was 70.5 (2.3)% and 60.7 (3.2)% at 3 and 7 years, respectively. Overall, the median (range) time from TUR to RC was 1.8 (0.3–11.6) months. The interval to RC analysed as a continuous or categorical variable was not associated with extravesical or nodal disease, lymph node metastases, disease recurrence, overall or cancer-specific survival. The results were similar in the subgroup of 320 patients (54%) with clinically muscle-invasive disease.

CONCLUSIONS

These results suggest that a reasonable delay from the last TUR to RC is not independently associated with stage progression or with decreased recurrence-free or disease-specific survival. These findings might have important implications for trial design in the ongoing evaluation of neoadjuvant regimens. Nevertheless, we see no reason to advocate anything less than the timely consideration of definitive treatment for patients with high-risk bladder cancer.

KEYWORDS

time, stage, bladder cancer, cystectomy, recurrence, survival

INTRODUCTION

Bladder cancer is a potentially lethal disease that often demands a radical and aggressive treatment approach. The decision to proceed to a life-altering major surgical procedure is complicated, unique to each patient. Several factors impose an inevitable but variable period of delay from presenting symptoms to diagnosis, and subsequently to definitive treatment. These include preoperative medical evaluation, the pursuit of additional therapeutic opinions, limitations of surgical schedules, and patient psychological factors. Intuitively, it might be presumed that excessive prolonging of this period might allow disease progression, resulting in an

unfavourable prognosis. Indeed, several authors reported that a delay of >3 months between transurethral resection (TUR) and radical cystectomy (RC) results in adverse clinical outcomes [1–3]. Nevertheless, in the light of limitations of these studies, we hypothesized that a reasonable delay in the interval from last TUR to RC would not affect cancer control by a clinically or statistically significant margin. Thus we evaluated the effect of the duration between TUR and RC on disease progression to more advanced disease stages, and on recurrence-free and disease-specific survival in a large group of patients with bladder TCC treated at three tertiary referral centres in the USA.

PATIENTS AND METHODS

We reviewed the records of 958 consecutive patients who had RC and pelvic lymphadenectomy with curative intent by selected surgeons at The University of Texas Southwestern, The Johns Hopkins Hospital, and The Baylor College of Medicine between 11 March 1984 to 24 January 2003. For each patient, comprehensive clinical and pathological information were collected and entered into an institutional review board-approved database. Many internal and external data reviews and quality checks were used to assure the accuracy and completeness of the data elements.

Our analysis was limited to patients who had TCC of the bladder, and therefore 67 with other than TCC histology were excluded from the analyses. We excluded patients undergoing salvage RC after primary chemoradiation (11) and those undergoing neoadjuvant chemotherapy (24) or radiotherapy (12). The treatment delay was defined as the interval from the last TUR to RC; the last TUR date and/or pathology were not available in 285 patients, leaving 592 patients for analysis.

Genitourinary pathologists at each site examined all specimens according to institutional protocols. The 1997 TNM classification was used for pathological staging, and the 1992 WHO classification for pathological grading. Clinically muscle-invasive (CMI) disease was defined as clinical stage \geq T2. The extravesical pathological stage was defined as \geq pT3N0 or pT(any)N > 0. Lymphovascular invasion was defined as the unequivocal presence of tumour cells within an endothelium-lined space with no underlying muscular walls. To ensure the validity of the pathological outcomes, two clinicians read the pathology reports of 219 consecutive patients, while unaware of patient clinical variables and the finding of the other reviewer. Inter-reader reliability was measured using the intraclass correlation coefficient, and was >0.95 for all pathological variables.

The follow-up was conducted according to institutional protocols. Patients were generally seen after RC at least quarterly for the first year, semi-annually for the second, and annually thereafter. Diagnostic imaging of the upper tracts and chest radiography were done at least annually or when clinically indicated. Detection of cancer in the ureter and/or urethra was coded as a second (metachronous) primary and not as local or distant recurrence. When patients died the cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Disease recurrence was defined as the development of either a local recurrence or distant metastasis. Most patients who were identified as having died of bladder cancer had progressive, widely disseminated, and often highly symptomatic metastases at the time of death. Death within 30 days of surgery was censored at time of death for cancer-specific survival analyses.

Fisher's exact test and the chi-squared test were used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across dichotomous or ranked categories were assessed using the Mann-Whitney *U*-test and the Kruskal-Wallis nonparametric ANOVA, respectively. Spearman's rank correlation coefficient was used to compare ordinal and continuous variables. The Kaplan-Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. For multivariate survival analyses we used the Cox proportional hazard regression model. Statistical significance was indicated at $P < 0.05$ (all reported values being two-sided).

RESULTS

The median (range) patient age was 66.4 (33.8–89.2) years; for all patients the median time interval from TUR to RC was 1.8 (0.3–11.6) months. The mean (SD) number of lymph nodes removed at RC was 18.2 (8.1); 118 patients (21.3%) had metastases to regional lymph nodes, and in these patients the median number of positive lymph nodes and mean percentage of positive lymph nodes were 2 (interquartile range, IQR, 4) and 13% (IQR 20), respectively.

Patients who ultimately had pathological non-muscle-invasive cancer (192, 35%) had a longer median time from TUR to RC than those with pathological muscle-invasive cancer (361, 65%; 1.83 vs 1.73 months, $P = 0.034$). There was no difference in the median time from TUR to RC between patients with organ-confined tumours (294, 53%) and those with extravesical tumours in the cystectomy specimen (259, 47%; 1.80 vs 1.73 months, $P = 0.230$). To further analyse the patients, three distinct pathological risk groups were created: organ-confined and lymph node negative (\leq pT2 N0, 294; 54%) vs extravesical and lymph node negative (\geq pT3 N0, 132; 24%) vs lymph node positive (pTany N+, 118, 22%). There was no difference in time from TUR to RC among these three risk groups ($P = 0.441$).

Patients were then categorized into those who had a lower pathological stage than clinical stage (i.e. pathological down-staging; 103, 19%), those who had the same clinical and pathological stage (187, 38%), and those who had a higher pathological stage than

clinical stage (i.e. pathological upstaging; 236, 43%). The median time from TUR to RC was not statistically different ($P = 0.078$) among patients who were pathologically down-staged (1.73 months, IQR 1.37), those who had the same clinical and pathological stage (1.63 months, IQR 1.5), and those who were pathologically up-staged (1.9 months, IQR 1.3).

The time from TUR to RC was weakly correlated with age at the time of surgery ($r = 0.084$, $P = 0.049$) but not the number of lymph nodes examined ($r = -0.106$, $P = 0.628$). In patients with metastases to lymph nodes, the time from TUR to RC was not associated with the number of positive nodes ($r = 0.086$, $P = 0.360$) or percentage of positive nodes ($r = 0.114$, $P = 0.229$).

In all, 459 patients (83%) had RC within 3 months of the last TUR and 96 (17%) did so at ≥ 3 months after the last TUR. There was no difference in the median age between the two groups ($P = 0.416$). The median time from TUR to RC was 1.6 (0.3–2.9) months in patients who had RC < 3 months after TUR, and 4.1 (3–11.6) months in those who had RC at ≥ 3 months. The association between this dichotomous description of the interval as a categorical variable and clinicopathological characteristics in all patients is shown in Table 1. Patients who had RC within 3 months from TUR were more likely to have pathologically muscle-invasive disease than those who had RC at ≥ 3 months after TUR (67% vs 55%, $P = 0.023$). There was similarly a greater proportion of patients with extravesical disease in the group with the shorter delay (49% vs 36%, $P = 0.025$).

The disease recurred in 186 patients (34%) and 214 (38%) had died at the time of analysis. The cause of death was missing in 28 patients (5%). Of the remaining patients, 136 (24%) died from bladder cancer and 50 (9%) died from other causes with no evidence of disease recurrence. The median (mean, SD, range) follow-up was 34.6 (45.0, 36.6, 0.5–183.4) months for patients alive at the last follow-up. The mean (SD) actuarial recurrence-free probabilities were 61.6 (2.4)% and 54.9 (2.9)%, and the actuarial bladder cancer-specific survival probabilities were 70.5 (2.3)% and 60.7 (3.2)%, at 3 and 7 years after RC, respectively.

In univariate Cox regression analyses, the time from TUR to RC analysed as a continuous

TABLE 1 The association of time from TUR to RC, as a continuous or categorical variable stratified by 3 months, in all patients and in those with CMI disease, with clinical and pathological characteristics

Variable	N (%)	TUR to RC, months		TUR to RC > or <3 months, n (%)			
		All Median (range), P	CMI Median (range), P	All <3	>3, P	CMI <3	>3, P
N patients		592	320	592		320	
Gender							
Female	107 (19)	1.70 (0.3–7.4)	1.43 (0.3–5.8)	89 (19)	18 (8)	60 (21)	9 (26)
Male	448 (81)	1.80 (0.3–11.6), 0.444	1.73 (0.3–6.8), 0.398	370 (81)	78 (92), 1.000	225 (79)	26 (74), 0.518
Pathological stage							
T0 (no tumour)	35 (6.3)	1.80 (0.4–10.5)	1.77 (0.4–6.3)	26 (6)	9 (9)	15 (5)	3 (9)
Ta	14 (2.5)	2.20 (0.3–4.1)	2.43 (1.6–3.2)	10 (2)	4 (4)	3 (1)	1 (1)
Tis	71 (12.8)	2.18 (0.3–15.4)	1.92 (0.7–3.2)	54 (12)	17 (18)	13 (5)	1 (1)
T1	72 (13.0)	1.82 (0.3–19.5)	1.77 (0.4–4.5)	59 (13)	13 (14)	21 (7)	3 (9)
T2	134 (23.4)	1.77 (0.3–26.0)	1.43 (0.3–5.1)	106 (23)	24 (25)	75 (27)	10 (29)
T3	167 (30.1)	1.83 (0.3–35.9)	1.80 (0.3–5.8)	146 (32)	21 (22)	116 (41)	14 (40)
T4	64 (11.5)	1.63 (0.3–11.3), 0.352	1.47 (0.3–6.8), 0.231	56 (12)	8 (8), 0.178	40 (14)	3 (9), 0.877
Pathological grade							
0 (no tumour)	35 (6.3)	1.80 (0.4–10.5)	1.76 (0.4–6.3)	26 (6)	9 (9)	15 (5)	3 (9)
1	2 (0.4)	2.73 (1.4–4.1)	–	1 (0.2)	1 (1)	0	0
2	37 (6.7)	1.60 (0.3–5.0)	1.43 (0.3–3.2)	33 (7)	4 (4)	15 (5)	2 (6)
3	480 (86.5)	1.83 (0.3–11.6), 0.147	1.77 (0.3–11.6), 0.415	398 (87)	82 (85), 0.228	254 (89)	30 (85), 0.720
Lymphovascular invasion							
Present	198 (35.7)	1.67 (0.3–10.5)	1.67 (0.3–6.8)	171 (38)	27 (28)	131 (47)	16 (47)
Absent	345 (62.2)	1.83 (0.3–11.6), 0.086	1.73 (0.3–6.3), 0.630	277 (62)	68 (72), 0.078	149 (53)	18 (53), 1.000
Metastases to lymph nodes							
Present	118 (21.3)	1.72 (0.3–7.3)	1.71 (0.3–4.6)	101 (22)	17 (18)	79 (28)	7 (21)
Absent	427 (76.9)	1.80 (0.3–11.6), 0.684	1.72 (0.3–6.8), 0.983	350 (78)	77 (82), 0.410	203 (72)	27 (79), 0.358

variable was not associated with disease recurrence, bladder cancer-specific death, or death from all causes ($P=0.213$, 0.118 , and 0.105 , respectively). Kaplan-Meier analyses showed no statistical difference in the risk of disease recurrence, disease-specific mortality, or overall mortality between patients who had RC within 3 months vs >3 months after the last TUR ($P=0.445$, 0.323 and 0.833 , respectively) (Fig. 1).

We repeated all the above analyses in the subgroup of patients who had CMI disease on TUR (320, 54%). The clinicopathological characteristics of this subgroup of patients are presented with those of the entire group in Table 1. The median interval between TUR showing muscle invasion and RC was 1.70 (0.3–6.8) months. In all, 285 patients (89%) had RC within 3 months and 35/320 (11%) had RC at >3 months after TUR.

Among patients with CMI, the time from TUR to RC, either as a continuous or categorical variable, was not associated with any of the clinicopathological characteristics

assessed (Table 1). The time from TUR to RC, either as a categorical or continuous variable, was not associated with pathological stage stratified into non-muscle-invasive vs muscle-invasive ($P=0.134$) or organ-confined vs extravesical ($P=0.585$; Table 2). Of 173 patients who were pathologically up-staged (56%), 85 had the same clinical and pathological stage (27%) and 60 were pathologically down-staged (19%). The time from TUR to RC, either as a categorical or continuous variable, was not associated with pathological up-staging ($P=0.381$).

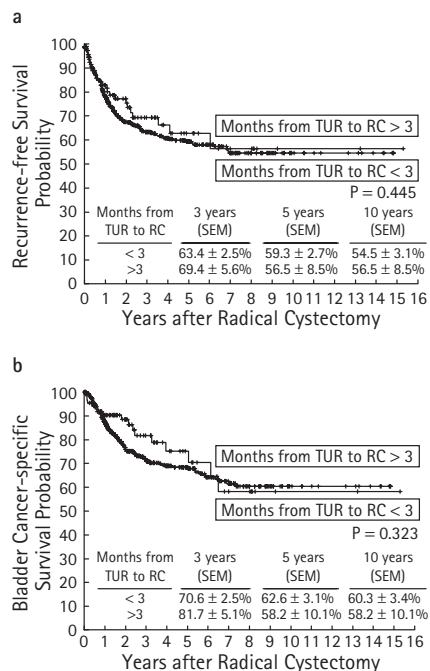
The disease recurred in 135 of the 320 patients (42%) and 143 (45%) had died at the time of analysis, 95 (30%) from bladder cancer. The median (mean, SD, range) follow-up was 33.9 (44.8, 34.9, 0.5–178.1) months for patients alive at the last follow-up. The time from TUR to RC, as a categorical or continuous variable, was not associated with bladder cancer recurrence ($P=0.749$ and 0.817 , respectively) or bladder cancer-specific survival ($P=0.862$ and 0.775 , respectively).

DISCUSSION

The issue of timing in surgical oncology is controversial and complex, influenced by factors both within and outside of the control of providers. Several recent reports suggest a significantly poorer prognosis for patients undergoing RC at >3 months after the diagnosis of muscle invasion [1–3]. Within this context we examined the outcome of a large group of patients treated by several surgeons at three tertiary referral centres.

We examined the association between the interval from TUR to RC and pathological outcome, disease recurrence and bladder cancer-specific survival in nearly 600 patients. Among this group, 320 patients had an additional separate evaluation for their presenting indication of CMI disease. We found no significant association between an increased delay from TUR to RC and pathological upstaging, extravesical disease, lymph node metastases, disease recurrence or bladder cancer-specific survival, examining the interval as both a continuous and dichotomous variable with a threshold of

FIG. 1. Kaplan-Meier estimates of recurrence-free (a) and bladder cancer-specific survival (b) probabilities according to time from TUR to RC, stratified by > or <3 months for 592 patients treated with RC and bilateral lymphadenectomy.



3 months after TUR. The absence of an association was consistent in both the group as a whole and in the subgroup presenting with CMI disease.

There is some controversy in published reports about the prognostic significance of an increasing delay to treatment in bladder cancer. Among historical series, this concept was first reported by Wallace and Harris [4] over 40 years ago, where they found a 35% survival advantage at 3 years for patients treated within a month of presentation. Subsequent studies found the opposite effect of timing, and actually found a preponderance of adverse clinical features among patients receiving the earliest treatment [5,6]. While not specifically addressing the focus of the present study, the question of the interval from presentation to RC in these early series raises two interesting points. The first is the possibility of a selection bias favouring patients with more adverse risk profiles for earlier RC, i.e. treating the more desperate cases relatively earlier. The second is the issue of the interval from disease presentation to surgery. These authors examined the time from initial symptomatic

TABLE 2 Association of the interval from TUR to RC with pathological features of the cystectomy specimen in all patients and in those with CMI disease (clinical stage ≥T2)

Variable	Interval from TUR to RC	
	Continuous Median, months (P)	Categorical, % <3 months >3 months (P)
All patients		
Muscle-invasive (≥pT2)	1.73 (0.034)	67 55 (0.023)
Non-muscle-invasive (<pT2)	1.83	33 45
Organ-confined (≤pT2N0)	1.80 (0.230)	51 64 (0.025)
Extravesical (≥pT3Nany)	1.73	49 36
Pathological downstaging	1.73 (0.078)	19 19 (0.812)
Equivalent to clinical stage	1.63	28 31
Pathological upstaging	1.90	53 50
CMI disease		
Muscle-invasive (≥pT2)	1.67 (0.134)	82 77 (0.498)
Non-muscle-invasive (<pT2)	1.80	18 23
Organ-confined (≤pT2N0)	1.65 (0.585)	39 43 (0.405)
Extravesical (≥pT3Nany)	1.73	61 57
Pathological downstaging	1.80 (0.158)	19 20 (0.493)
Equivalent to clinical stage	1.43	26 34
Pathological upstaging	1.73	56 46

presentation to treatment as the indicator of treatment delay, whereas contemporary series have generally evaluated the interval from diagnosis to definitive treatment as the indicator variable. It is likely that the initial period in the course of clinical disease, starting at the point of an indication for diagnostic evaluation, is of substantial prognostic importance.

Several recent series specifically examined the delay from a diagnosis of muscle invasion to RC, with some general consistency of results. Sanchez-Ortiz *et al.* [1] found an interval of >12 weeks between a diagnosis of muscle invasion and RC to be associated with advanced pathological stage and decreased 3-year survival among 189 patients having RC for muscle-invasive disease. One major limitation of their series was that only 19 patients had a delay of >12 weeks, and among them, three waited 2–3 years and three waited >3 years before RC. Delays of this magnitude in a substantial proportion of the subgroup probably unfavourably biased the outcomes for their patients with a delay of >12 weeks. Similar findings were presented shortly thereafter by Chang *et al.* [2] in their experience with 153 patients. They found that patients with a delay of >90 days had a significantly higher incidence of extravesical disease (81% vs 52%). Survival outcomes were not analysed, nor did they use multivariate analyses. May *et al.* [3] reported

the outcomes of 189 patients stratified by whether they had surgery within 3 months of the diagnosis of muscle invasion. They found that the 42 patients with >3 months delay were significantly older, had a significantly greater incidence of pT4 tumours and decreased progression-free survival on univariate regression analysis. An interval of >3 months was not associated with extravesical or node-positive disease, and was not an independent predictor of disease recurrence in multivariate analysis. Most recently, a large population-based study from Quebec found poorer overall survival among patients with a delay of >12 weeks from TUR to RC, but these authors did not address disease-specific survival, and nor did they account for potential confounding clinicopathological features or adjuvant treatments [7].

By contrast with these reports, we found that the interval from the last TUR to RC was not predictive of an adverse outcome, whether expressed as a continuous or categorical variable, in all patients undergoing RC and in the subgroup with the indication of CMI disease. A recent series from Sweden reported similar findings but was limited to the extent that 13% of patients did not have a lymphadenectomy and 33% of patients received neoadjuvant radiation [8]. The present series has the advantages of statistical power, having the most patients

with clinicopathological data available to address this question, and less confounding from differences in patient age or case mix.

The timing of RC for patients with high-risk superficial disease is complex and controversial. Herr and Sogani [9] reviewed the Memorial Sloan-Kettering experience, reporting the results of 90 patients initially managed with TUR and intravesical BCG, and who ultimately had RC over 15–20 years of follow-up. Patients who had RC within 2 years had significantly better disease-specific survival than patients with a delay of >2 years from initial diagnosis. The present data for patients with superficial disease are somewhat limited, in that the TUR history reflects the most recent TUR and not necessarily the initial diagnosis of superficial disease or the chronology of interventions in patients with polychronotropic disease.

The present study has several limitations; first and foremost are those inherent to retrospective analyses. We do not have information on the timing of initial symptomatic presentation relative to diagnosis and subsequent definitive therapy, and nor do we have information on the reasons for the delay to RC, including coexisting comorbidities, i.e. the study used the date of the last TUR, not the initial diagnostic TUR, as the nearest time point. This is an important distinction between our study and others. Sanchez-Ortiz *et al.* [1] and May *et al.* [3] each found that the seeking of second opinions predominated among their patients as reasons for delay, but Sanchez-Ortiz *et al.* also had significantly older patients in their cohort with a delay of >3 months, raising the possibility that the evaluation of a greater burden of comorbid disease might have been important in their findings. We excluded the relatively few patients who received neoadjuvant radiation or chemotherapy and therefore cannot comment on the effect of these in this context. Furthermore, as mentioned above, limitations in our data for the subgroup of

patients with superficial disease limit our ability to place the analysis of that subgroup in the context of more detailed relevant studies [9].

Although there was no significant adverse prognostic effect with an increasing interval from TUR to RC, we do not advocate undue delay in seeking definitive therapy for patients with clear indications. High-risk bladder cancer is a potentially lethal disease mandating a serious and timely consideration of effective management options appropriate for the individual patient. Future directions include prospective studies evaluating the question of optimal timing for patients with particular prognostic features. Over time, these questions might be better informed by integrating molecular prognostic tools currently under active development. Finally, the issue of timing with regard to the prognostic significance of the interval from initial symptomatic presentation to diagnosis and definitive therapy, beyond the scope of the present study, might offer fertile ground for better understanding the natural history of bladder cancer, and ongoing studies of screening protocols for high-risk populations might substantiate additional important prognostic information in this area.

CONFLICT OF INTEREST

None declared.

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Abbreviations: TUR, transurethral resection; RC, radical cystectomy; CMI, clinically muscle-invasive; IQR, interquartile range.