Cystectomy Delay More Than 3 Months From Initial Bladder Cancer Diagnosis Results in Decreased Disease Specific and Overall Survival

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Purpose: Some groups hypothesize that a delay in cystectomy may result in higher pathological stage and possibly alter survival in patients with bladder cancer. The timing of this delay has been somewhat arbitrary. We evaluated the timing from T2 bladder cancer diagnosis to cystectomy, its impact on survival and potential causes of delay.

Materials and Methods: A contemporary cohort of 214 consecutive patients presented with clinical T2 bladder cancer and underwent radical cystectomy as primary therapy. Clinicopathological parameters were maintained in an institutional database. A review of time to cystectomy, pathological stage, disease specific survival and OS was performed. Variables were tested in univariate and multivariate analyses. The log rank test was used for exploratory analyses to determine meaningful delay cutoff points.

Results: Mean followup and time to cystectomy in the entire cohort was 40 months and 60 days, respectively. A significant disease specific survival and OS advantage was observed in patients undergoing cystectomy by 93 days or less (3.1 months) compared to greater than 93 days ($p = 0.05$ and 0.02, respectively). Pathological staging was similar between the groups ($p = 0.15$). A multivariate benefit in OS was observed in patients treated with timely cystectomy. The most common factor contributing to cystectomy delay was scheduling delay, as seen in 46% of cases.

Conclusions: A cystectomy delay of 3.1 months undermines patient survival, likely through the development of micrometastases, since local stage progression is not apparent at this point. Most delays are avoidable and should be minimized. Despite the need for second opinions and the impact of busy surgical schedules clinicians must strive to schedule patients efficiently and complete surgical treatment within this time frame.

Key Words: bladder, cystectomy, bladder neoplasms, mortality

Cystectomy remains the gold standard for muscle invasive bladder cancer, resulting in a 5-year DSS of up to 74% to 81%.[1,2] Naturally any cancer treatment should be delivered expediently. Delayed medical, surgical and radiation therapy may contribute to greater recurrence, stage progression and decreased survival.[3–8] Recent data suggest that the timing of cystectomy is critical in the treatment of muscle invasive bladder cancer with a cystectomy delay approaching 3 months potentially resulting in pathological up staging and decreased survival.[9–12]

Although a cystectomy delay of 3 months intuitively could offer a deleterious outcome, a rationale for this cutoff point is not clearly supported in the current literature. Consequently reports reflect analyses at 12 weeks and 90 days. Based on these data a cystectomy delay of 84 to 90 days has been associated with more advanced pathological stage,[9–11] increased incidence of vascular invasion,[6] and decreased OS[3,6] and progression-free survival.[11] Although it is of significant interest, portions of these data are limited by small populations, an arbitrary time cutoff and no assessment of DSS. Furthermore, some conflict exists about the impact of a cystectomy delay on pathological staging.

We addressed these limitations by first determining an appropriate cutoff point for cystectomy delay in a contemporary population. Like others, we hypothesize that there is a time point at which cystectomy delay contributes to more aggressive pathological features and potentially impacts survival. We specifically addressed the impact of cystectomy delay on DSS and OS. Furthermore, we extended the studies of others by examining the cause of cystectomy delay to minimize future therapeutic delay in this patient population.

MATERIALS AND METHODS

From August, 1990 to November, 2004, 712 patients underwent radical cystectomy at our institution. Of them 214 consecutive patients presented with an initial diagnosis of clinical T2 bladder cancer and underwent radical cystectomy as primary therapy. These 214 patients comprise the cohort of this study. Pelvic node dissection was performed in all except 22 patients (10%). Preoperative staging was based on clinical pathological findings, abdominal imaging with computerized tomography or magnetic resonance imaging and examination with the patient under anesthesia, when avail-

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able. Bone scan was done if patients had bulky tumors, bony symptoms or increased alkaline phosphatase. Patients underwent standard postoperative surveillance.[13]

Patient information was collected in a database approved by the University of Michigan Institutional Review Board. The clinicopathological parameters evaluated were patient age, sex, time to cystectomy, ASA classification, pathological stage,[14] lymphovascular invasion, DSS and OS. The cause of treatment delay was attributable to physician factors (scheduling delays, misdiagnosis or reluctance to offer therapy) and patient factors (prolonged treatment decision making, domestic/social issues, comorbidities and seeking multiple physician opinions). The cause for delay was gleaned from the patient record in retrospective fashion with attention given to nursing and triage notes as well as to physician notes.

Survival intervals were defined as time from cystectomy to time of death related to bladder cancer (DSS) or to time of death by any cause (OS). Patients were censored at the date of last followup if they were alive or dead of other/unknown causes (DSS), or alive (OS). Cystectomy delay was defined as time from initial diagnosis to time of cystectomy. To determine a cutoff point for the cystectomy delay variable that was relevant to DSS and OS we examined all possible daily delay intervals in the range of this cohort, essentially dividing the cohort into 2 populations at each time point. Log rank analyses then detected any possible survival difference between the 2 populations. A relevant cutoff point was defined as one resulting in a statistically significant survival difference measured at that cutoff point and consistently at subsequent cutoff points.

The earliest significant cutoff point was used to divide the population into patients undergoing cystectomy with a delay of less than or equal to the cutoff point and those with a delay of greater than the cutoff point. Clinicopathological parameters were compared between the 2 groups. Organ confined bladder cancer included pathological stage Ta, Tis, T1 and T2, all with N0M0, and extravesical disease included pathological T3, T4 and T any N+ or M+ tumors.

The bivariate relationships between patient categories and clinicopathological parameters were retrospectively assessed using the Mantel-Haenszel chi-square test. The univariate effect of time to cystectomy on OS and DSS was estimated using the log rank test and Kaplan Meier estimates. The multivariate relationship between key factors (age, sex, time to cystectomy, pathological stage and ASA) and survival was assessed using Cox regression modeling to determine factors that had any significant independent effect on OS and DSS. A logistic model was created to determine the factors (age, sex, time to cystectomy and ASA) that had any significant independent effect on the likelihood of extravesical tumor. Since lymphovascular invasion information was only available on 72% of the population, it was not included on multivariate analyses. The 5% significance level was applied to all tests and models. Analyses were performed using the SAS system (SAS Institute, Cary, North Carolina).

RESULTS

Table 1 lists cohort demographics. Median time to cystectomy was 61 days (2.0 months). The cystectomy delay interval was 4 to 175 days, including 4 to 42 in 64 patients, 43 to 84 in 107 patients, 85 to 126 in 33 patients and 127 to 175 in 10 patients.

TABLE 1. *Patient demographics and clinicopathological parameters*

	Entire Cohort	Delay (days)		p Value
		93 or Less	Greater Than 93	
No. pts (%)	214	188 (88)	26 (12)	
Mean followup ± SE (mos)	40 (2.8)	40 (3.0)	42 (10.0)	0.85
Mean age	65	65	66	0.57
Mean time to cystectomy ± SD (days)	61 (1.0)	53 (0.7)	124 (0.7)	<0.001
No. sex (%):				
Male	162 (76)	141 (75)	21 (81)	0.63
Female	52 (24)	47 (25)	5 (19)	
No. ASA (%):*				
1	7 (4)	7 (4)	0	0.04
2	119 (56)	106 (68)	13 (57)	
3	52 (24)	43 (28)	9 (39)	
4	1 (less than 1)	0	1 (4)	
No. pathological stage (%):				
Organ confined	85 (40)	78 (41)	7 (27)	0.15
Extravesical	129 (60)	110 (59)	19 (73)	
No. pathological T stage (%):				
T0	26 (12)	23 (12)	3 (12)	0.85
Ta	2 (1)	1 (1)	1 (4)	
Tis	11 (5)	8 (4)	3 (12)	
T1	9 (4)	8 (4)	1 (4)	
T2	51 (24)	49 (26)	2 (8)	
T3	92 (43)	80 (43)	12 (46)	
T4	23 (11)	19 (10)	4 (15)	
No. pathological N stage (%):				
Nx/N−	156 (73)	137 (73)	19 (73)	0.98
N+	58 (27)	51 (27)	7 (27)	
No. lymphovascular invasion (%):†				
Present	55 (35)	49 (36)	6 (33)	0.84
Absent	100 (65)	88 (64)	12 (67)	

* Total of 32 patients did not have information available.
† Total of 59 patients did not have information available, including 27% and 31% with cystectomy delay of 93 or less and greater than 93 days, respectively.

A survival comparison of patients treated before and after each possible delay cutoff point revealed similar DSS and OS when cystectomy was delayed from 4 to 92 days ($p = 0.19$ to 0.97). A delay of 93 days resulted in a DSS and OS disadvantage in those treated after this point ($p = 0.05$ and 0.02, respectively, table 2). In our study population survival was similar in patients with a delay cutoff point of 84 days (12 weeks) and of 90 days ($p = 0.25$ and 0.11, respectively, table 2). The majority of cutoff points after 93 days continued to demonstrate survival advantages in those treated earlier than the cutoff point. The most pronounced survival difference was observed at a delay of 124 days for OS and at a delay of 151 days for DSS ($p = 0.003$ and 0.008, respectively).

Figures 1 and 2 further show the survival advantage in patients with a cystectomy delay interval of 93 days or less. In the entire cohort 87 patients died of any cause, including 39% of those with a delay of 93 days or less and 54% of those with a greater than 93-day delay, whereas 55 died of bladder cancer, including 25% of those with a delay of 93 days or less and 35% of those with a greater than 93-day delay. Median DSS in those with a delay of 93 days or less was not attained but in those treated at greater than 93 days it was 1.0 years.

TABLE 2. *Log rank analysis of disease specific and overall survival stratified by select delay periods*

Cystectomy Delay (days)	No. Pts		Survival p Value	
	Equal or Less Delay	Greater Delay	Disease Specific	Overall
84 (12 wks)	171	43	0.32	0.25
85	171	43	0.32	0.25
86	172	42	0.20	0.11
87	172	42	0.20	0.11
88	172	42	0.20	0.11
89	173	41	0.19	0.10
90	178	36	0.12	0.11
91 (13 wks)	181	33	0.14	0.09
92	185	29	0.19	0.11
93	188	26	0.05	0.02
94	189	25	0.04	0.01
95	189	25	0.04	0.01
96	189	25	0.04	0.01
97	189	25	0.04	0.01
98 (14 wks)	189	25	0.04	0.01

Three-year DSS was 62% and 49%, respectively. Median OS in those with a delay of 93 days or less and greater than 93 days was 3.4 and 0.9 years, and 3-year overall survival was 51% and 38%, respectively.

Table 1 also shows a comparison of clinicopathological parameters in patients undergoing cystectomy before or after 93 days. The 2 populations had similar age, followup and sex distributions. Mean time to cystectomy was longer in the population with the extended delay (<0.001). Likewise the extended delay population had a higher proportion of comorbidities with 43% classified as ASA 3 or 4 compared to 28% with ASA 3 or 4 in the group treated in 93 days or less (p = 0.04). Pathological parameters and local staging were similar between the 2 populations.

In the multivariate survival models patients with a cystectomy delay of greater than 93 days were at 96% increased risk for death from any cause and at 112% increased risk for death from bladder cancer compared to patients with a cystectomy delay of 93 days or less (p = 0.04 and 0.08, respectively, table 3). Pathological T and N stage classifications were significant predictors of OS and DSS with more advanced tumors associated with worse survival compared with noninvasive primary tumors (pT0/pTa/pTis) or with no nodal involvement (N0). An ASA classification of 3 also predicted decreased OS and DSS compared to an ASA classification of 1. A multivariate model designed to predict

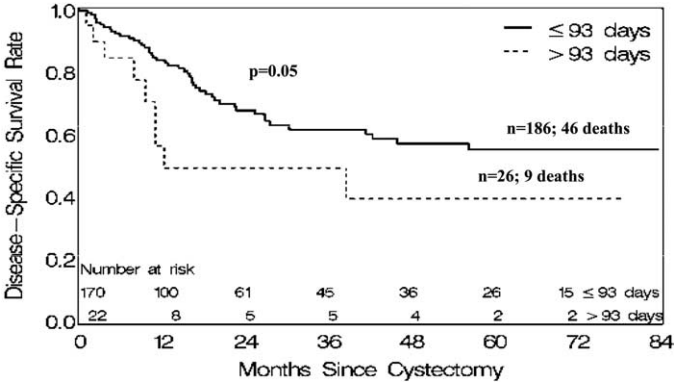

FIG. 1. Kaplan-Meier curves using log rank test for post-cystectomy DSS in patients with primary bladder carcinoma stratified by time to cystectomy (93 days or less vs greater than 93).

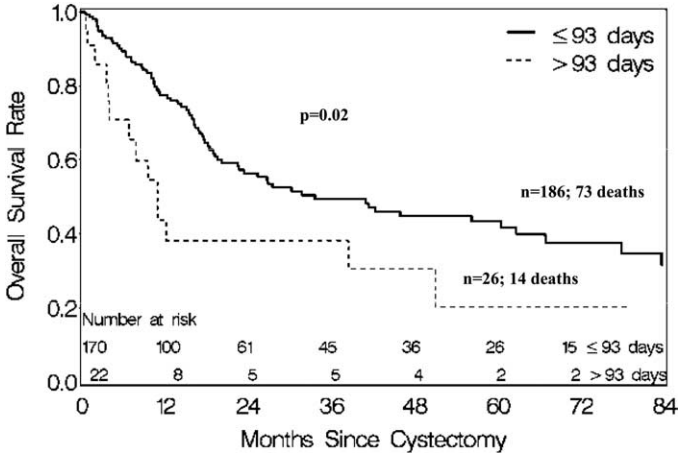

FIG. 2. Kaplan-Meier curves using log rank test for post-cystectomy OS in patients with primary bladder carcinoma stratified by time to cystectomy (93 days or less vs greater than 93).

nonorgan confined pathology suggested that a cystectomy delay of greater than 93 days did not predict clinically evident extravesical tumor compared to a delay of 93 days or less (p = 0.27). No parameter predicted extravesical disease except an ASA score of 3, which was associated with nonorgan confined pathology compared to an ASA of 1 (HR 4.8, p = 0.02).

Figure 3 shows the apparent etiologies of delayed cystectomy in 26 patients who underwent cystectomy after 93 days. Scheduling delays related to clinical or research appointments were observed in 46% of this group. Multiple opinions, social issues and misdiagnosis or reluctance to treat were infrequent causes of delay and each occurred in only 1 patient (4%). Patient comorbidities and difficulty with decision making occurred in 4 (15%) and 3 patients (12%), respectively.

DISCUSSION

Oncological treatment is most effective when delivered expeditiously. Several examples in the literature support this intuitive contention for systemic and localized therapies. In patients with locally advanced or early metastatic prostate cancer delayed androgen ablation results in decreased survival after radiation, prostatectomy and observation.[6–8] Delayed adjuvant radiotherapy may result in increased local recurrence in breast, and head and neck cancers.[3] Furthermore, delayed surgery can result in pathological up staging of lung cancer.[4] Thus, it stands to reason that the delivery of cystectomy in more timely fashion could also improve survival in patients with muscle invasive bladder cancer.

In the current study all potential time points were explored to determine a relevant cutoff point. A survival disadvantage in nonadjusted DSS and OS was demonstrated when cystectomy was delayed by 3.1 months after the diagnosis of muscle invasive bladder cancer. Moreover, this point of treatment delay resulted in decreased adjusted OS. A trend toward decreased adjusted DSS was also observed, reflecting a 10% higher rate of death from bladder cancer in the group with a prolonged cystectomy delay (fig. 1). Small patient subsets may have limited multivariate analyses. Ultimately the cutoff point of 3.1 months was consistent with arbitrarily determined cutoff points in the literature.

TABLE 3. *Cox proportional hazard model for bladder cancer specific and overall mortality risk*

		Bladder Ca Specific Mortality		Overall Mortality	
	Referent	HR	p Value	HR	p Value
Age at diagnosis*		0.99	0.27	1.00	0.96
Gender: female	Male	1.12	0.75	1.46	0.15
ASA:	1				
2		2.58	0.38	3.59	0.22
3		8.99	0.05	12.32	0.02
4		7.12	0.21	8.23	0.16
Pathological T stage:	T0/Ta/Tis				
T1		7.78	0.09	7.64	0.006
T2		2.21	0.27	1.46	0.39
T3		5.74	0.005	2.74	0.009
T4		11.56	<0.001	7.15	<0.001
Pathological N stage:	N0				
NX		2.50	0.03	1.78	0.07
N1		3.54	0.001	2.34	0.01
N2		2.96	0.01	2.25	0.02
N3		12.97	<0.001	8.57	0.002
Cystectomy delay greater than 93 days:	93 Days or less	2.12	0.08	1.96	0.04

Existing evidence supports an association between cystectomy delay and altered survival. Sánchez-Ortiz et al noted significant improvement in adjusted DSS in patients treated with timely cystectomy.[9] Patients treated during 12 weeks (84 days) were at almost twice the risk for death than those treated at or within 12 weeks. The increased treatment delay likely had more impact in this population, which included up to 31% clinical stage T3 and T4 cases. Hara et al determined that a cystectomy delay of 3 months (90 days) resulted in a 35% decrease in unadjusted disease-free survival, DSS and OS but the delay interval lost significance on multivariate analyses.[12] Likewise May et al reported a 21% lower progression-free survival rate in patients with a cystectomy delay of greater than 3 months.[11] The delay interval ultimately lost significance on multivariate analyses, although there appeared to be a trend toward improved survival for more timely cystectomy. To our knowledge the current study is the first to demonstrate a multivariate benefit in overall survival in clinical T2 cases treated with timely cystectomy, albeit with a cutoff point obtained in exploratory fashion.

Although our population did not demonstrate significantly altered survival at the 84 and 90-day cutoff points, the similarity in delay periods is quite close and, thus, a 3-month cutoff point would be a reasonable delay limit for clinicians to target. Differences between our population and others[9,10] may be related to our exclusion of patients known to have a need for a cystectomy delay (neoadjuvant chemotherapy). Most cases excluded for this cause were believed to be clinical T3 because of hydronephrosis on imaging, a mass on examination using anesthesia, or highly suspicious findings on computerized tomography or magnetic resonance imaging.

Why should a delay in cystectomy impact survival? The intuitive response would be that extended time without treatment would result in tumor progression. Therefore, local progression measured by pathological T and N stage classification is reasonable and important to assess. Although others detected more advanced local pathological stage in patients with delayed cystectomy,[10] we did not observe evidence of significant local tumor progression in our population, although 14% more patients with a delay of more than 3.1 months had nonorgan confined disease. This was further confirmed on multivariate analysis, when cystectomy delay did not predict extravesical disease. Our findings of a survival disadvantage without significant local tumor progression echo a smaller series of Hara et al that showed disadvantages in recurrence-free survival, DSS and OS in patients treated primarily with cystectomy more than 3 months after initial diagnosis compared to those treated within 3 months of diagnosis.[12] There was little difference in local pathological staging between the groups. Although the small sample size of the greater than 93-day delay group in the current series may have contributed to decreased statistical power, it is still clear that this sample size had enough power to demonstrate a survival difference, although it just met our definition of statistical significance for DSS ($p < 0.05$). Nonetheless, this sample size is a limitation of the study. It is likely that tumor progression is a contributing factor but probably less so in terms of local stage. Presumably a more predominant factor is driving the survival difference.

Micrometastatic spread may be this factor. Micrometastases are not detectable by contemporary imaging and, thus, they were not readily quantifiable by this study. However, a delay in primary local control might ultimately lead to an increased rate of micrometastases, similar to what has been experienced with testis cancer. The striking difference in median survival between patients with a delay of 93 days or less (not yet attained) and those with a delay of greater than 93 days (1 year) may be consistent with this hypothesis. The short (1-year) median DSS in patients with a cystectomy delay of greater than 93 days is consistent with median survival in patients with known metastatic bladder disease.[15–17] It is possible that additional information may be gleaned through a comparison of sites of recurrence in pa-

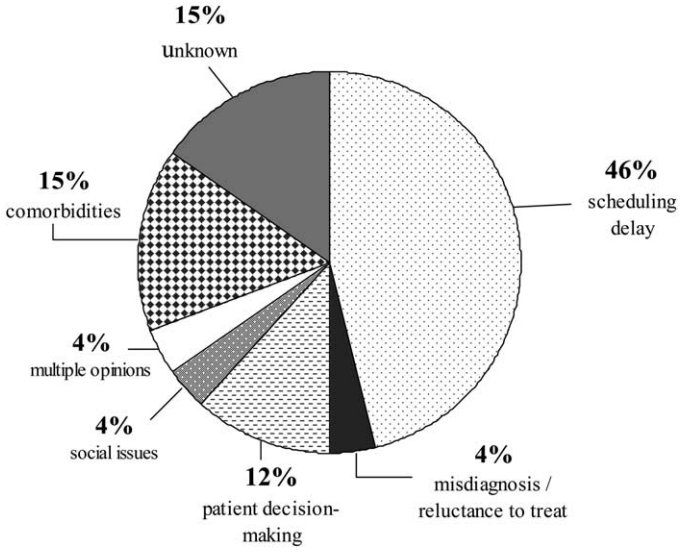

FIG. 3. Causes of cystectomy delay in 26 patients treated more than 93 days from initial bladder cancer diagnosis.

tients with and without delayed cystectomy. In the current series the small number of total recurrence events in the greater than 93-day group (9) prohibited meaningful comparisons of local, distant and urothelial recurrence sites with the 93-day or less group.

One may question why cystectomy delay should increase the risk of distant micrometastases but not be associated with an increase in pelvic nodal spread. We speculate that a relationship may exist between micrometastases and vascular invasion, as demonstrated in breast cancer.[18] Vascular invasion and lymphatic invasion may be facilitated by different factors and cystectomy delay may promote earlier vascular spread compared to lymphatic spread. In support of this is the increased rate of vascular invasion detected by others in patients with cystectomy delayed more than 3 months.[12] In the current series the diagnosis of isolated vascular invasion was not available, although rates of lymphovascular invasion were similar between delay groups. This issue is the subject of ongoing study.

It is clear, then, that cystectomy delay has serious consequences for muscle invasive tumors. Several factors may contribute to this delay and it is important to examine them. Irreversible factors potentially contributing to cystectomy delay are patient age and comorbidity. In this data set patient age was similar between those undergoing more expedient cystectomy and those experiencing some delay and, thus, it did not contribute significantly to delay. In contrast, patient comorbidity may have impacted the timing of treatment since patients with a prolonged time to cystectomy had a higher proportion of ASA 3 and 4 categories. Comorbidity was the second highest cause of delay, affecting at least 15 % of patients.

Most causes of cystectomy delay in our population were potentially reversible. Almost half of the delays resulted from nonredundant physician scheduling, including delayed clinic appointments due to provider case load or unavoidable absence. Coordinating multiple visits for preoperative counseling and medical clearance was difficult at times and this is an area where increased coordination is needed. Office visits to determine eligibility for research studies or complete entry criteria also contributed to delay, although this represented a small number of patients. Patient indecision about treatments was an uncommon cause of delay.

This retrospective data set is limited, in that patient factors and comorbidity may be underestimated. If patients delayed cystectomy because of indecision or treatment fear, they may have ultimately elected an alternative treatment and, thus, they would not have been included in this study. Similarly if comorbidities resulted in a lack of medical clearance or high risk medical clearance, patients again may have sought nonsurgical treatments. Another potential limitation is related to the definition of survival interval, which started from the time of cystectomy and not from the initial diagnosis of muscle invasive bladder cancer. This definition could potentially introduce an artificial lead time bias against patients with a cystectomy delay. However, if one assumes that cystectomy can alter the natural history of clinical T2 bladder cancer, post-cystectomy survival is a reasonable end point when considering whether the timing of cystectomy is important.

CONCLUSIONS

A cystectomy delay of 3.1 months undermines patient survival. This may be related to the development of micrometastases since local tumor progression is not clearly evident at this point. Most delays are avoidable and should be minimized. Despite the need for second opinions and the impact of busy surgical schedules clinicians must strive for expedient referral, rigorous coordination of preoperative counseling and medical clearance, and detailed patient education to permit an efficient decision making process and timely delivery of surgery.

Abbreviations and Acronyms

ASA	=	American Society of Anesthesiologists
DSS	=	disease specific survival
OS	=	overall survival

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EDITORIAL COMMENT

Muscle invasive bladder cancer is a morbid condition and the optimization of therapy depends on meticulous attention to multiple clinical and technical parameters. This report adds further weight to the importance of surgical timing as another of the important determinants in achieving good outcomes. Prior studies alluded to the value of performing cystectomy in an approximate 3-month window to avoid deterioration of survival outcomes (references 9 to 12 in article). In this investigation only clinical T2 cases were included, which provides some further insight into the possible mechanism of this alteration in outcome based on time to surgery. While not proven, it is suggested that microscopic metastasis may contribute to the changes seen, given that there was no significant stage migration during the period of time delay. Like the others cited, this investigation has a relatively small group of patients (26) who were delayed in their time to surgery but an impact on this delay cohort is noted and the time frame of about 3 months as a significant delay is again demonstrated. It is interesting to note that in this series scheduling issues were a significant issue in delaying surgery in more than 40% of the delayed group. In other series second opinions and medical optimization of less fit surgery candidates drove the situation toward delay. Recognition of scheduling issues provides a more remediable solution to the entire problem. With the greater use of neoadjuvant chemotherapy before cystectomy it is also tempting to consider whether this approach will obviate the concern of delayed therapy by addressing issues of systemic disease, and yet there is also the possibility that poor responders to chemotherapy will be under served by a delay in time to surgery. This analysis further consolidates the opinion that with radical surgery, as in comedy, timing counts if one wishes to get the best outcome.

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