



Bladder Cancer

Outcome of Patients Who Refuse Cystectomy after Receiving Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer

Harry W. Herr*

Department of Urology, Memorial Sloan-Kettering Cancer Center, Weill-Cornell Medical College, 1275 York Avenue, New York, NY 10021, USA

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Abstract

Objectives: To determine the outcome of patients who refuse cystectomy after receiving neoadjuvant chemotherapy for muscle-invasive bladder cancer.

Methods: Between 1995 and 2001, 63 patients were evaluated who declined to undergo a planned cystectomy, because they achieved a complete clinical response to neoadjuvant cisplatin-based chemotherapy. Patient, tumor, and treatment features were assessed prospectively, and correlated in univariate and multivariate analyses with overall survival. The median follow-up was 86 mo and all patients were followed for more than 5 yr.

Results: Forty patients (64%) survived, with 54% of them having an intact functioning bladder. The number and size of invasive tumors were strongly associated with overall survival. The most significant treatment variable predicting better survival was complete resection of the invasive tumor on re-staging transurethral resection before starting chemotherapy. Of 23 patients (36%) who subsequently died of disease, 19 (30%) relapsed with invasive cancer in the bladder. Over 90% of surviving patients had solitary, small, and low-stage invasive tumors completely resected, and 83% survived without relapses in the bladder.

Conclusions: Selected patients with muscle-invasive bladder cancers may survive after transurethral resection and neoadjuvant chemotherapy, and tumor features can identify which patients responding completely to chemotherapy may survive without cystectomy.

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* Tel. +1 646 422 4411; Fax: +1 212 988 0768.

E-mail address: herrh@mskcc.org.

1. Introduction

Randomized clinical trials and inclusive meta-analyses show that a combination of neoadjuvant chemotherapy and cystectomy improves survival of patients with muscle-invasive bladder cancer over radical surgery alone [1]. Chemotherapy aims to treat undetected metastases, and radical cystectomy provides the best local control of the primary tumor. Most survivors achieve major responses to chemotherapy and have an increased likelihood of having no residual tumor (pT0) in the cystectomy specimen [2]. In one study, 38% of surgical specimens after chemotherapy were pathologically free of cancer compared with 15% after cystectomy, and 85% of the patients with a pT0 specimen survived 5 yr [3]. What remains unknown is whether patients who have pathological pT0 tumors after chemotherapy would have survived without the subsequent cystectomy?

For more than a decade, patients who are fit candidates for cystectomy have received neoadjuvant chemotherapy. Radical cystectomy and a pelvic lymph node dissection are advised even if they respond favorably to chemotherapy, because only a third of patients are pathologically free (pT0) of cancer, and transurethral biopsies and computed tomography (CT) scans often fail to detect microscopic disease in the bladder, pelvis, and lymph nodes that might be cured by radical surgery [4]. A few patients, however, refuse cystectomy after chemotherapy, especially if they have major responses in the bladder, and their outcome has not been documented. This study reports the fate of a cohort of patients with muscle-invasive bladder cancers who declined definitive surgery after achieving a complete clinical response to neoadjuvant chemotherapy. It also aims to determine whether tumor features before treatment can identify patients who are most likely to survive without cystectomy.

2. Methods

From 1995 to 2001, 63 selected patients were referred for cystectomy of a muscle-invasive bladder cancer discovered on an initial transurethral resection (TUR) biopsy performed by the referring urologist. Review of outside pathological slides confirmed invasion of the muscularis propria of the bladder wall. Each patient then underwent examination under anesthesia and a contemporary re-staging (second) TUR by the author, documenting the presence of residual muscle-invasive bladder cancer. Staging CT scans of chest, abdomen, and pelvis were consistent with a localized, non-metastatic bladder cancer.

Neoadjuvant chemotherapy was recommended because of persistent muscle invasion, and each patient received at least four cycles of a cisplatin-based regimen. The response was evaluated several weeks after completion of chemotherapy by another TUR biopsy and CT scan; the treatment plan was then to proceed with planned cystectomy. However, the 63 patients refused cystectomy and wished to be followed, because no tumor was found on postchemotherapy TUR biopsy and CT scans showed shrinkage of tumor in the bladder, including resolution of hydronephrosis and palpable mass.

The patients have been followed every 3–6 mo with repeat cystoscopies and TURs as needed to detect and treat bladder tumor recurrences, and with CT scans to detect pelvic or systemic relapse. Recurrent noninvasive tumors in the bladder were treated with intravesical Bacillus Calmette-Guérin. Patients who recurred with invasive bladder tumors were advised to undergo salvage cystectomy. Patient data were entered prospectively in an institutional review board-approved database, and updated each visit for tumor recurrence and treatment events.

At the initial evaluation on the basis of a bimanual examination under anesthesia, re-staging TUR pathology, and CT scan, tumors were clinically staged as confined to the bladder (cT2) or spread outside the bladder (cT3–4). Also noted was the number of invasive tumors (solitary or multiple), tumor configuration (papillary or solid), tumor size (<5 cm or >5 cm), presence of a palpable mass, carcinoma in situ (CIS), hydronephrosis, lympho-vascular invasion in the primary tumor, and a history of prior noninvasive bladder tumors. The re-staging (second) TUR was performed 2–6 wk after the initial TUR, and aimed to resect all visible or suspected muscle-invasive cancer. If muscle tissue contiguous to the lateral and deep margins of the primary site of invasion was microscopically negative for tumor, the resection was considered to be complete. If tumor was present in biopsies of deep muscle or fat adjacent to the primary tumor mass, the resection was considered incomplete. Patients who had no cancer or had noninvasive cancer found on re-staging TUR were excluded from this study. Only patients who had muscle-invasive cancer on the second TUR received neoadjuvant chemotherapy.

The primary end point of the study was overall survival. The median follow-up time was 86 mo (95%CI, 75–96), and all patients have been followed for a minimum of 5 yr. Associations between patient and tumor variables and survival were evaluated by Pearson chi-square tests. Kaplan-Meier curves for overall survival were constructed and compared with the use of the log-rank test. Patients who were alive at last follow-up or died of other causes were censored at that point. A Cox proportional hazards regression model was used to identify independent variables predictive of overall survival. All tests were two-sided and *p* values less than 0.05 were considered significant.

3. Results

Table 1 shows the patients' and tumor characteristics. The median age was 62 yr. Each patient had operable bladder cancer, was sufficiently healthy to

Table 1 – Patient and tumor characteristics

Variable	No. of patients (%)
Patients	63
Sex	
Male	47 (75%)
Female	16 (25%)
Age (yr)	
Median (range)	62 (32–79)
<65	37 (59%)
>65	26 (41%)
Tumor stage ^a	
cT2	36 (57%)
cT3–4	27 (43%)
No. of invasive tumors	
Single	44 (70%)
Multiple	19 (30%)
Prior superficial bladder tumors	
No	39 (62%)
Yes	24 (38%)
Tumor configuration	
Solid	53 (84%)
Papillary	10 (16%)
Tumor size	
<5 cm	43 (68%)
>5 cm	20 (32%)
Hydronephrosis	
No	54 (86%)
Yes	9 (14%)
Palpable mass	
No	47 (75%)
Yes	16 (25%)
Carcinoma in situ	
No	43 (68%)
Yes	20 (32%)
Re-staging TUR	
Complete	29 (46%)
Incomplete	34 (54%)
Lymphovascular invasion	
No	28 (44%)
Yes	35 (56%)
Chemotherapy regimen	
MVAC	51 (81%)
Other ^b	12 (19%)
No. patients cT0 after chemotherapy ^c	63
Relapse in bladder	
No	23 (36%)
Yes	40 (64%)
Bladder stage at relapse	
Muscle invasive	24 (38%)
Non-muscle invasive	16 (25%)

TUR, transurethral resection; MVAC, methotrexate, vinblastine, adriamycin, cisplatin.

^a Clinical stage, organ-confined (T2) vs. extravesical (T3–4) tumor.

^b Gemcitabine + cisplatin or ifosfamide, Taxol, cisplatin combination.

^c cT0, negative postchemotherapy TUR biopsy.

undergo radical surgery, received at least 85% of the planned four cycles of cisplatin-based chemotherapy, achieved complete clinical response with negative TUR biopsies of the primary tumor site (cT0), and refused cystectomy. They were also declined the offer to receive radiation therapy. Of the 63 patients, 40 (64%) have survived without metastatic disease and 23 (36%) have died of bladder cancer.

Table 2 shows prognostic factors associated with overall survival. Advanced tumor stage (cT3), more than one or a large-size invasive tumor incompletely resected portended reduced survival on univariate analysis. A multivariate analysis identified a single invasive tumor, smaller size (<5 cm) tumor, and complete resection as significant pretreatment variables favorably associated with overall survival. Recurrence of a muscle-invasive tumor in the bladder also correlated with worse survival. A multivariate analysis for bladder relapse showed multiple invasive tumors, large (>5 cm) tumor size, and less than a complete TUR predicted systemic relapse and a worse survival.

Fig. 1A and B show overall survival and overall survival with preserved bladder. With a median follow-up of 86 mo for all 63 patients, 64% were alive and 54% of the survivors had an intact, normally functioning bladder. The mean survival time was 108 mo (range, 60–120) for survivors and 32 mo (range, 12–48 mo) for patients who died of disease.

Fig. 2 shows overall survival according to whether patients had a complete or incomplete resection of the original bladder tumor. Of the 29 patients having complete resection on re-staging TUR, 93% survived (mean survival time, 113 mo; 95%CI, 103–122) compared with 38% of 34 patients who survived after incomplete TUR (median survival, 36 mo; 95%CI, 23–48) ($P < 001$). Two patients died of bladder cancer after a complete TUR; they had more than one invasive tumor, clinically advanced (cT3) disease, and relapsed with invasive bladder cancer in the first year of follow-up.

Fig. 3 shows the overall survival by bladder relapse and stage. Forty of the 63 patients (64%) had recurrent tumors in the bladder, which was muscle-invasive in 24 (38%) and noninvasive in 16 (25%). Tumors recurred at the site of the original tumor in half the cases (23 patients) and were located in other areas of the bladder in half (17 patients). The median time to muscle invasion was 16 mo (range, 7–30) and was 17 mo (range, 6–44) for noninvasive tumors. Of 16 patients with noninvasive tumor recurrences, 94% survived (mean survival, 114 mo; 95%CI, 103–125). One patient progressed to local invasion and eventually

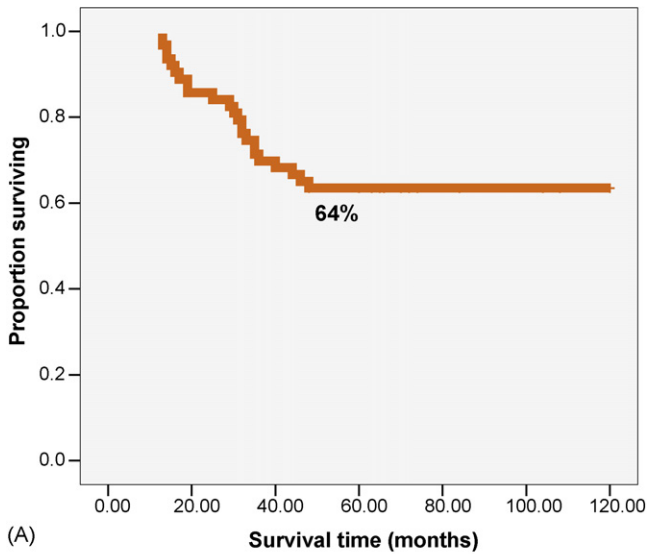
Table 2 – Prognostic factors for overall survival of all 63 patients

Variable	No. alive (%)	Univariate <i>p</i>	Hazard ratio	95%CI	Multivariate <i>P</i>
All patients	40 (64%)				
Sex		0.02	0.23	0.05–10.1	0.07
Male	25 (53%)				
Female	15 (94%)				
Age (yr)		0.43	10.0	0.99–10.1	0.17
<65	25 (68%)				
>65	15 (58%)				
Tumor stage		0.03	10.5	0.81–20.8	0.19
cT2	28 (78%)				
cT3–4	12 (44%)				
No. of tumors		0.001	90.9	30.4–160.5	<0.001
Single	35 (80%)				
Multiple	5 (26%)				
Prior tumors		0.23	10.1	0.41–20.8	0.89
No	27 (69%)				
Yes	13 (54%)				
Tumor shape		0.64	0.36	0.1–10.3	0.13
Solid	33 (62%)				
Papillary	7 (70%)				
Tumor size		0.004	50.6	10.8–160.6	0.01
<5 cm	31 (72%)				
>5 cm	9 (45%)				
Hydronephrosis		0.21	10.4	0.37–40.8	0.64
No	36 (67%)				
Yes	4 (44%)				
Palpable mass		0.06	10.8	0.55–50.9	0.33
No	33 (70%)				
Yes	7 (44%)				
CIS		0.34	0.84	0.32–20.2	0.71
No	29 (67%)				
Yes	11 (55%)				
Restaging TUR		0.001	60.5	10.2–150.8	0.02
Complete	27 (93%)				
Incomplete	13 (38%)				
LVI		0.52	0.78	0.30–20.0	0.61
No	19 (68%)				
Yes	21 (60%)				
CT regimen		0.15	0.69	0.29–10.6	0.39
MVAC	31 (61%)				
Other	9 (73%)				
Bladder relapse		0.02	0.74	0.18–30.1	0.69
No	19 (83%)				
Yes	21 (53%)				
Stage at relapse		<0.001	20.2	0.98–50.1	0.05
Invasive	6 (25%)				
Noninvasive	15 (94%)				

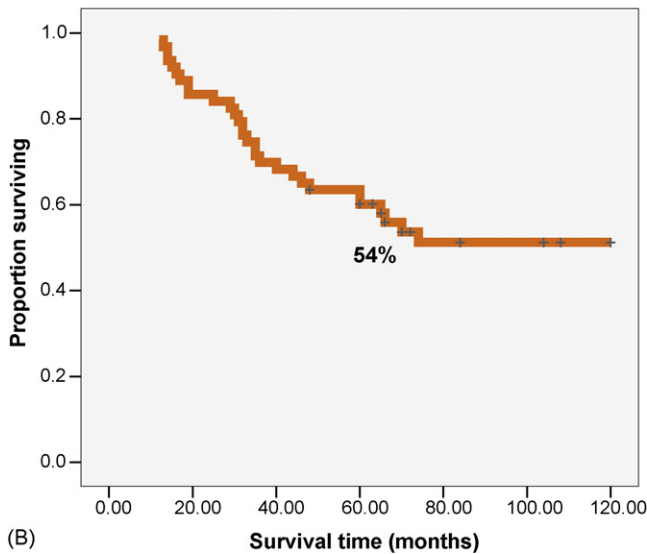
95% CI, 95% confidence interval; CIS, carcinoma in situ; TUR, transurethral resection; LVI, lymphatic vessel invasion; CT, computed tomography; MVAC, methotrexate, vinblastine, adriamycin, cisplatin.

succumbed to disease. Of 24 patients who recurred with a muscle-invasive cancer, 25% survived (median survival, 39 mo; 95%CI, 31–48) and 18 died of disease. Ten patients refused cystectomy even after

invasive tumors recurred and eventually died of disease. Fourteen patients underwent cystectomy, of whom 6 were salvaged and 8 patients subsequently died of bladder cancer. Of the 23 patients



(A)



(B)

Fig. 1 – (A) Overall survival for all 63 patients. (B) Overall survival with preserved bladder for all patients; salvage cystectomy was taken as an additional event.

(36%) who suffered no relapse in the bladder, 83% survived (mean survival, 103 mo; 95%CI, 88–118), and 4 patients died of metastatic disease alone.

A total of 23 patients (36%) died of disease, including 19 who relapsed first in the bladder. If we assume that all 19 patients would have survived had they undergone their planned postchemotherapy cystectomy, then the added mortality risk of refusing early cystectomy was 30% (19 of 63 patients). The majority of patients who eventually died of disease had adverse tumor features, including clinical extravesical (cT3–4) tumors (70%), multiple invasive primary tumors (61%), incomplete tumor resections (91%), palpable mass and larger tumors (52%), prior history of bladder tumors (63%), hydronephrosis

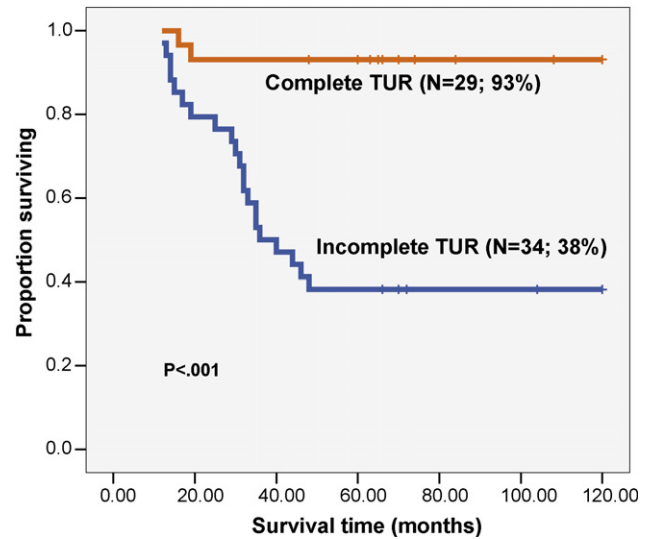


Fig. 2 – Overall survival by re-staging transurethral resection (TUR).

(39%), or relapse in the bladder during the first follow-up year (83%). On the other hand, of the 34 patients who remained alive with an intact bladder, the majority had tumors that were clinically confined (cT2) to the bladder (74%), solitary tumors (94%), tumors less than 5 cm in size (74%), a complete resection (62%), no palpable mass (82%), absence of hydronephrosis (85%), and no history of prior bladder tumors (77%).

4. Discussion

The major finding of the study is that 64% of 63 patients who refused cystectomy after achieving

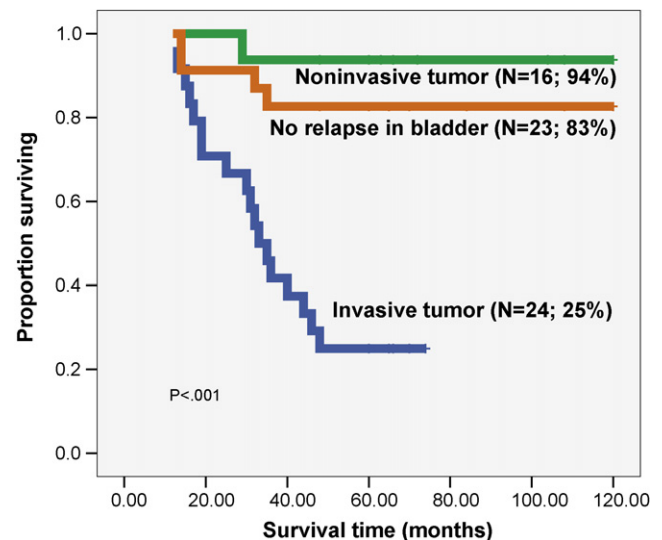


Fig. 3 – Overall survival by bladder relapse and stage.

a complete response of a muscle-invasive bladder cancer to neoadjuvant chemotherapy survived at least 5 yr, and 54% of the survivors had an intact functioning bladder. Relapse in the bladder occurred in the majority of patients (64%), resulting in an additional 30% disease-related mortality, assuming optimistically that all such patients would have been spared by a timely postchemotherapy radical cystectomy. Patients refusing cystectomy after chemotherapy might jeopardize their survival owing to lack of definitive treatment of the primary bladder tumor as well as the risk of developing new invasive tumors in the bladder.

Patients most likely to relapse in the bladder and die of their cancer had multiple or large tumors that clinically were not confined to the bladder, and thus were less amenable to microscopic complete transurethral resection. Further, delayed cystectomy salvaged fewer than half of the patients relapsing with persistent or a new invasive bladder cancers. Patients having such tumor features, despite responding completely to chemotherapy, should be strongly advised to undergo planned cystectomy, because the risk of untreated pelvic tumor or later invasion in the bladder is high, often leading to premature death. Even aggressive TUR of locally advanced bladder cancers after chemotherapy cannot reliably detect residual microscopic disease in deep muscle or perivesical fat, nor in pelvic lymph nodes.

On the other hand, with attention to detail, certain tumor features can identify suitable patients who are likely to survive without cystectomy if they have no sign of disease after chemotherapy. These include patients who have tumors clinically confined to the bladder that can be visibly and microscopically resected completely before neoadjuvant treatment. Transurethral resection is a stochastic procedure subject to many variables and is difficult to quantify. These variables include the quality of resection and pathological assessment of disease in multiple and difficult-to-orient biopsy specimens. Attempts to reduce the uncertainty included aggressive TURs before and after chemotherapy, based on the insistence that visibly complete resections be verified by microscopic clear margins of TUR specimens. Such patients usually had only a scar visible on postchemotherapy TUR biopsy of primary tumor sites rather than evidence of carcinoma. Although even favorable patients remain at risk for new tumors in the bladder, these survival results suggest that close follow-up rather than immediate cystectomy may be a reasonable option for highly selected patients.

The median age of these patients was 62 yr, a decade younger than the 72 yr among our cystectomy candidates, and more than half (59%) were younger than 65 yr of age. The major reason patients gave for declining cystectomy, despite improved quality of life associated with continent bladder substitution, was not only preservation of the bladder but also sexual function. Although understandable, younger patients have most to lose if primary therapy fails to control their disease. None of the patients deferred cystectomy because of toxicity to chemotherapy.

Prior studies have shown that some invasive bladder cancers can be cured by TUR alone [5], neoadjuvant chemotherapy and TUR [6,7], or by combined-modality therapy incorporating radiation [8]. These studies, however, included significant numbers of patients who had non-muscle-invasive cancers or did not have a re-staging TUR to assess local extent of disease before chemotherapy. In contrast, our study had residual muscle invasion even on re-staging TUR, likely explaining why resection status emerged as a significant variable for survival, even when adjusted for a complete clinical response (cT0) to chemotherapy. Among patients with resectable invasive tumors, chemotherapy, combined with radiation, achieves comparable survival to cystectomy, and tri-modality therapy is an important and effective alternative for such patients [9].

We [10,11] and others [12,13] have suggested that individual or multiple molecular markers may identify tumors that are more likely to respond to chemotherapy and to select patients for bladder preservation. So far, analyses of putative tumor markers have been retrospective, and none has been validated prospectively in clinical trials. This study suggests that tumor features can be measured and used to identify patients with muscle-invasive bladder cancers who are likely to survive without cystectomy when treated by systemic chemotherapy and aggressive endoscopic surgery. Molecular profiles will need to be integrated in robust clinical trials adjusted for such tumor features to prove useful in selecting patients for bladder preservation. A national cooperative trial is underway to test the value of tumor markers and treatment of muscle-invasive bladder cancers by chemotherapy and transurethral resection.

5. Conclusions

Half the patients whose muscle-invasive bladder cancer responded completely to neoadjuvant

chemotherapy survived and preserved their bladder. Either the TUR or the chemotherapy, or both, may have contributed to complete tumor control, but since all patients had residual muscle invasion when first treated, it is likely chemotherapy played a major role. The most significant variables predicting both overall and bladder-preserved survival was an early-stage and unifocal tumor, in which a visible and microscopic complete resection was accomplished.

Conflicts of interest

The author has nothing to disclose.

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