Radical Cystectomy in the Treatment of Invasive Bladder Cancer: Long-Term Results in 1,054 Patients

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Purpose: **To evaluate our long-term experience with patients treated uniformly with radical cystectomy and pelvic lymph node dissection for invasive bladder cancer and to describe the association of the primary bladder tumor stage and regional lymph node status with clinical outcomes.**

Patients and Methods: **All patients undergoing radical cystectomy with bilateral pelvic iliac lymphadenectomy, with the intent to cure, for transitional-cell carcinoma of the bladder between July 1971 and December 1997, with or without adjuvant radiation or chemotherapy, were evaluated. The clinical course, pathologic characteristics, and long-term clinical outcomes were evaluated in this group of patients.**

Results: **A total of 1,054 patients (843 men [80%] and 211 women) with a median age of 66 years (range, 22 to 93 years) were uniformly treated. Median follow-up was 10.2 years (range, 0 to 28 years). There were 27 (2.5%) perioperative deaths, with a total of 292 (28%) early complications. Overall recurrence-free survival at 5 and 10 years for the entire cohort was 68% and 66%, respectively. The 5- and 10-year recurrence-free survival for patients with organ-confined, lymph node–negative tumors was 92% and 86% for P0 disease, 91% and 89% for Pis, 79% and 74% for Pa, and 83% and 78% for P1 tumors, respectively. Patients with muscle invasive (P2 and P3a), lymph node–negative tumors had 89% and 87% and 78% and 76% 5- and 10-year recurrence-free survival, respectively. Patients with nonorgan-confined (P3b, P4), lymph node–negative tumors demonstrated a significantly higher probability of recurrence compared with those with organ-confined bladder cancers ($P < .001$). The 5- and 10-year recurrence-free survival for P3b tumors was 62% and 61%, and for P4 tumors was 50% and 45% , respectively. A total of 246 patients (24%) had lymph node tumor involvement. The 5- and 10-year recurrence-free survival for these patients was 35%, and 34%, respectively, which was significantly lower than for patients without lymph node involvement ($P < .001$). Patients could also be stratified by the number of lymph nodes involved and by the extent of the primary bladder tumor (p stage). Patients with fewer than five positive lymph nodes, and whose p stage was organ-confined had significantly improved survival rates. Bladder cancer recurred in 311 patients (30%) . The median time to recurrence among those patients in whom the cancer recurred was 12 months (range, 0.04 to 11.1 years). In 234 patients (22%) there was a distant recurrence, and in 77 patients (7%) there was a local (pelvic) recurrence.**

Conclusion: **These data from a large group of patients support the aggressive surgical management of invasive bladder cancer. Excellent long-term survival can be achieved with a low incidence of pelvic recurrence.**

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BLADDER CANCER is the second most common genitourinary malignancy, with transitional-cell carcinoma (TCC) comprising nearly 90% of all primary bladder tumors. It was estimated that 54,200 new patients would be diagnosed with bladder cancer in 1999 and that there would be 12,100 projected deaths from the disease.[1] Although the majority of patients present with superficial bladder tumors, 20% to 40% either present with or develop invasive disease.

Most TCCs that are or become invasive are high-grade tumors. These tumors originate in the bladder mucosa, progressively invade the lamina propria, and move sequentially into the muscularis propria, perivesical fat, and contiguous pelvic structures, with increasing incidence of lymph node involvement with progression.[2,3] During the past 30 years, radical cystectomy has emerged as one of the standard forms of therapy for patients with high-grade, invasive bladder cancer. However, early results of radical cystectomy indicated that only about 50% of patients treated for high-grade invasive disease were cured and that most patients subsequently died of metastatic disease within 3 years of diagnosis. Lack of universal acceptance of this procedure was attributable largely to the considerable morbidity, in particular the need for urinary diversion. During the 1960s and 1970s, in an effort to improve survival after cystectomy, various regimens of preoperative radiation

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were implemented but failed to demonstrate convincingly any additional benefit. Furthermore, the operation was associated with considerable morbidity.[4] Since the early 1980s, various protocols of single agent and combination chemotherapy trials have been proposed for use in the adjuvant setting for patients considered at high risk for developing metastasis based on pathologic findings at the time of cystectomy. Although the precise role of adjuvant or neoadjuvant chemotherapy in this setting has not been definitively established, results from small trials are encouraging.[5]

We have developed an aggressive surgical approach for patients with invasive TCC of the bladder. This includes en bloc cystectomy, bilateral pelvic iliac lymph node dissection, and some form of lower urinary tract reconstruction. Improvements in medical, surgical, and anesthetic therapy have clearly reduced the morbidity and mortality associated with contemporary surgery. Radical cystectomy also provides an accurate evaluation of the primary bladder tumor as well as the regional lymph nodes. This evaluation allows for adjuvant treatment strategies based on clear pathologic rather than clinical staging, the latter of which has been associated with significant errors in 30% to 50% of patients.[3,6,7] This, coupled with the evolution of continent urinary diversion, especially orthotopic lower urinary tract reconstruction to the native urethra, now provides both male and female patients a more acceptable means for storing and eliminating urine, thus lessening the impact of cystectomy on their quality of life.[8,9] We believe radical cystectomy with pelvic lymphadenectomy and orthotopic lower urinary tract reconstruction play a central role in the treatment of patients with invasive bladder cancer and provide excellent results with regard to survival and prevention of local recurrence. As the role of chemotherapy or other forms of adjuvant therapy are further defined in this setting, the long-term freedom from metastasis and overall survival will continue to improve.

We present our long-term surgical experience and clinical outcomes in a large group of patients treated with radical cystectomy for invasive TCC of the bladder.

PATIENTS AND METHODS

Indications for Cystectomy

The indication for radical cystectomy was based on cystoscopic and biopsy findings, including tumor invasion of the muscularis propria or prostatic stroma, high-grade, invasive bladder tumors associated with carcinoma-in-situ, carcinoma-in-situ refractory to intravesical chemotherapy or immunotherapy, or recurrent multifocal superficial disease refractory to repeat transurethral resection with/without intravesical therapy. Overall, 94% of patients undergoing cystectomy in this series demonstrated high-grade bladder tumors.

Patients

We have established a computerized cystectomy database at our institution containing detailed and comprehensive clinical and pathologic information about all patients who have undergone cystectomy since August 1971. We report on patients who underwent cystectomy for bladder cancer in 1997 or earlier; the records of 1,471 consecutive patients were identified in the database with a date of cystectomy on or before December 1997. Excluded from analysis were 72 patients undergoing cystectomy for other (nonbladder) pelvic malignancies, and 107 patients with non-TCC bladder cancers. These patients will be the subject of a separate report. Of the remaining 1,292 patients with primary TCC of the bladder, 126 underwent a salvage surgical procedure after failure of definitive radiation therapy ($\geq$ 5,000 rads), 23 were found to be inoperable at the time of exploration, 46 demonstrated distant metastases at the time of cystectomy, and 43 had evidence of gross disease remaining after cystectomy (never free of disease). All were excluded from this analysis. The intent of this analysis is to focus on a relatively homogenous cohort of patients with high-grade, invasive TCC of the bladder who achieved a complete resection of all grossly evident tumors at the time of cystectomy. The aforementioned exclusions may create biases; however, the analysis of a completed cystectomy with curative intent remains a critical topic.

The remaining 1,054 patients underwent radical cystectomy for primary TCC of the bladder with the intent to cure and are the focus of this analysis. Of these 1,054 patients, 843 were men (80%) and 211 were women. The median age was 66 years (range, 22 to 93 years).

Treatment

All patients underwent a previously described, standard surgical procedure, including a meticulous pelvic iliac lymphadenectomy with en bloc radical cystectomy, and urinary diversion.[10] The specific form of urinary diversion, either incontinent (conduit) or continent (cutaneous or orthotopic), is related primarily to the particular era in which the urinary reconstruction was performed (Table 1). A conduit form of diversion was replaced by a continent cutaneous form of reconstruction in 1982, with orthotopic reconstruction ultimately becoming the primary form of diversion at our institution for men in 1986[9] and for women in 1992.[11]

Adjuvant Therapy

The application of adjuvant therapies (radiation and/or chemotherapy) has evolved at our institution during the 26 years of patients treatment reported here. Although not the primary focus of this analysis, the role of adjuvant therapies remains an important component in the overall treatment of selected patients with high-grade, invasive bladder cancer.

Initially, the management of patients with bladder cancer included the planned administration of preoperative radiation. From 1971 to 1978, 97 patients received a high-dose short course of approximately 1,600 rads delivered over a 4-day period immediately preceding cystectomy. We compared the 97 patients who received a high-dose, short course of preoperative radiation therapy, followed by cystectomy (1971 to 1978), with 248 patients of similar pathologic stage who underwent cystectomy between 1979 and 1986 and who received no adjuvant radiation or systemic chemotherapy. Notwithstanding the limitations of nonrandomized comparison, this comparison revealed no significant difference in time to recurrence or overall survival between the two groups.[4] Furthermore, there was no difference in the incidence of pelvic recurrence. Preoperative radiation therapy has not been used routinely since 1979.

Table 1. Urinary Diversion at USC: 1971 to 1997

Time Period	Total No. of Patients	Form of Urinary Diversion							
		Conduit*		Ureterosigmoidostomy		Continent Cutaneous†		Orthotopic	
		No.	%	No.	%	No.	%	No.	%
1971 to 1981	164	148	90	16	10	0		0	
1982	38	34	89	1	3	3	8	0	
1983 to 1985	164	30	18	0		134	82	0	
1986	54	9	17	0		43	79	2	4
1987 to 1991	306	23	8	0		114	37	169	55
1992 to 1997	328	23	7	0		78	24	227	69
Total	1,054	267	25	17	2	372	35	398	38

*Including ileal and colon conduits.

†Including rectal reservoirs.

We administered chemotherapy selectively in 272 patients (26%) in an adjuvant setting from 1978 to the present: 211 patients received chemotherapy in an adjuvant (postoperative) setting after surgery based on pathologic analysis of the primary bladder tumor and regional lymph nodes, and 48 received this in a neoadjuvant (preoperative) setting before surgery. Thirteen patients received both chemotherapy and radiation therapy before surgery.

Pathology

All cystectomy specimens were examined by the same pathologic protocol. Multiple sections were obtained from the tumor, the bladder wall, and mucosa adjacent to and distant from the tumor, along with the ureters and regional lymph nodes. In men, tissue was obtained from the seminal vesicles and prostate. In women, sections were obtained from ovaries, uterus, and vagina when appropriate.

All bladder tumors were primary TCC, with some demonstrating prominent histologic features of glandular (7%) or squamous (11%) differentiation. Histologic grading was performed according to the method of Bergkvist.[12] Pathologic staging of the primary bladder tumor and lymph nodes was performed according to the 1987 tumor-node-metastasis (TNM) classification.[13] We are currently comparing the old (TNM) system to the 1997 TNM classification by the American Joint Committee on Cancer,[14] and this evaluation will be the subject of a future report.

Pathologic subgroups were defined as organ-confined, lymph node–negative tumors (P0, Pa, Pis, P1, P2, P3a), nonorgan-confined (extravesical), lymph node–negative tumors (P3b, P4), and lymph node–positive disease.

Follow-Up

All patients were followed postoperatively at 4-month intervals the first year, 6-month intervals the second year, and annually thereafter. Follow-up consisted of physical examination, along with routine serum chemistry studies including biochemical liver profile and alkaline phosphatase. Radiographic evaluation of the urinary diversion, upper urinary tracts (intravenous pyelography or ultrasonography), and chest radiography were performed at 4 months postoperatively, then annually thereafter unless otherwise clinically indicated. Elective bone scans and abdominal/pelvic computerized tomography scans were performed when clinically indicated.

The median follow-up for the entire cohort of 1,054 patients is 10.2 years; 91% of patients have 3 or more years of follow-up, with a maximum of 27 years.

Clinical Outcomes

Perioperative mortality (any death within 30 days of surgery or before discharge) and early complications (any complication within 3 months of surgery) were recorded. Complications were evaluated according to the administration of any preoperative therapy (radiation and/or chemotherapy) as well as by the form of urinary diversion (incontinent or continent) performed.

Outcomes were measured by time to clinical recurrence and overall survival. Time to clinical recurrence or recurrence-free survival was calculated as the time from cystectomy to the date of the first documented clinical recurrence or until last follow-up if the patient had not experienced a clinical recurrence; patients who died before clinical recurrence were censored at the time of death. Survival was calculated as the time from cystectomy to the date of death; all deaths regardless of cause, were counted as events; patients who are still alive were censored at the date of last contact.

Bladder cancer recurrences were classified as local (pelvic), distant (metastatic), or both. Local recurrences, by definition, occurred within the soft tissue field of exenteration. Distant recurrences were defined as those that occurred outside the pelvis.

Analysis of Results

Kaplan-Meier plots[15] were used to estimate the overall survival and recurrence-free survival for all 1,054 patients combined and for subgroups of patients classified by pathologic stage; standard errors were based on Greenwood's formula.[16] To estimate the chance of local or distant recurrence, the method of competing risks was used with local recurrence, distant recurrence, or death as the included competing failures.[17] The logrank test (overall[16] and stratified[18]) was used to compare subgroups of patients in terms of survival and time to recurrence. Pearson's χ^2 test for associations or the Mantel-Haenszel test for trend[19] were used to evaluate the association between clinical variables. All *P* values reported are two-sided.

RESULTS

Mortality

Perioperative death occurred in 27 (3%) of 1,054 patients. No obvious difference in mortality rate was observed in this series when evaluated by the form of urinary diversion performed: eight perioperative deaths among 278 patients

Table 2. Mortality and Morbidity With Radical Cystectomy and Urinary Diversion

Form of Urinary Diversion	No. of Patients	%	Perioperative Mortality*		Early Complication†	
			No.	%	No.	%
Preoperative adjuvant therapy						
Conduit‡	278	26	8	3	83	30
Continent§	776	74	19	2	209	27
None	884	84	26	3	247	28
Radiation only	108	10	1	1	30	30
Chemotherapy only	49	5	0		12	25
Radiation and chemotherapy	13	1	0		3	23
Total	1054		27	3	292	28

*Any death within 30 days of surgery or before discharge.
†Any complications within the first 4 months after surgery.
‡Including ileal and colon conduits.
§Including continent cutaneous, orthotopic, and rectal reservoirs.

(3%) undergoing an incontinent (conduit) form, and 19 (2%) of 776 patients undergoing a continent form of urinary diversion. In addition, no obvious difference in perioperative mortality was seen when stratified by the administration of preoperative therapy: 26 (3%) of 884 patients receiving no therapy, one (1%) of 108 patients receiving radiation only, none of the 49 patients receiving neoadjuvant chemotherapy only, and none of the 13 patients receiving both radiation and chemotherapy preoperatively (Table 2).

Morbidity

A total of 292 patients (28%) sustained an early complication. No apparent difference was observed in the early complication rate when evaluated by the form of urinary diversion: 83 (30%) of 278 patients undergoing an incontinent (conduit) form and 209 (27%) of 776 undergoing a continent form of urinary diversion. No obvious difference was observed in the early complication rate when stratified by the administration of preoperative therapy: 247 (28%) of 883 patients receiving no therapy, 30 (28%) of 108 patients receiving radiation only, 12 (25%) of 49 patients receiving neoadjuvant chemotherapy only, and three (23%) of 13 patients receiving both radiation and chemotherapy preoperatively (Table 2).

Pathologic Staging and Subgroups

Pathologic staging of the 1,054 patients included 808 patients (77%) without evidence of lymph node involvement: 66 patients (6%) with P0, 100 patients (9%) with Pis, 42 patients (4%) with Pa, 194 patients (18%) with P1, 94 patients (9%) with P2, 98 patients (9%) with P3a, 135 patients (13%) with P3b, and 79 patients (7%) with P4 tumors. Pathologic subgroups included 594 patients (56%) with organ-confined lymph node–negative tumors and 214 patients (20%) with nonorgan-confined (extravesical) lymph node–negative tumors (Table 3).

A total of 246 patients (23%) in this series were found to have lymph node–positive disease on pathologic analysis after cystectomy. Increasing incidence of lymph node involvement was found with increasing p stage of the primary bladder tumor. Lymph node–positive disease was found in 19 (5%) of 421 patients with superficial (P0, Pis, Pa, P1) primary bladder tumors (p stage). The incidence of lymph node involvement increased with muscle invasive primary bladder tumors: 21 (18%) of 115 patients with P2, and 35 (26%) of 133 patients with P3a disease. Lymph node–positive disease was highest in patients with nonorgan-confined primary bladder tumors; 113 (46%) of 248 patients with P3b, and 58 (42%) of 137 patients with P4 primary bladder tumors (Table 3).

Recurrence-Free and Overall Survival

The recurrence-free and overall survival for all 1,054 patients at 5 years was 68% and 66%, respectively, and it was 60% and 43%, respectively, at 10 years (Table 3, Fig 1). Most deaths occurring within the first 3 years after cystectomy were attributed to bladder cancer. However, with continued follow-up (after 3 years), most deaths in this elderly group of patients were related primarily to other comorbid diseases unrelated to bladder cancer.

Recurrence-free and overall survival for the entire cohort was significantly related to pathologic stage and lymph node status (Table 3, Fig 2). Increasing pathologic stage and lymph node–positive disease were associated with significantly higher recurrence rates and worse overall survival ($P < 0.001$). The probability that the 594 patients (56%) with organ-confined, lymph node–negative bladder tumors (P0, Pa, Pis, P1, P2, P3a) would remain recurrence-free was not statistically different when stratified by each individual

Table 3. Recurrence-Free and Overall Survival After Radical Cystectomy

Pathologic Stage*	No. of Patients	Probability of Surviving and Remaining Recurrence-Free ($P \pm$ SE)			
		Recurrence-Free		Overall Survival	
		5 Years	10 Years	5 Years	10 Years
Po, Pa, Pis					
N−#	208	.89 ± .02	.85 ± .03	.85 ± .03	.67 ± .04
N+s	5	.60 ± .22	.60 ± .22	.40 ± .22	.40 ± .22
All Pts PoPaPis	213	.88 ± .02	.85 ± .03	.84 ± .03	.67 ± .04
P1					
N−	194	.83 ± .03	.78 ± .04	.76 ± .03	.52 ± .04
N+	14	.43 ± .13	.43 ± .13	.50 ± .13	.42 ± .13
All Pts P1	208	.80 ± .03	.75 ± .04	.74 ± .03	.51 ± .04
P2					
N−	94	.89 ± .03	.87 ± .04	.77 ± .04	.57 ± .06
N+	21	.50 ± .11	.50 ± .11	.52 ± .11	.52 ± .11
All Pts P2	115	.81 ± .04	.80 ± .04	.72 ± .04	.56 ± .05
P3a					
N−	98	.78 ± .05	.76 ± .05	.64 ± .05	.44 ± .06
N+	35	.41 ± .09	.37 ± .09	.40 ± .08	.26 ± .08
All Pts P3a	133	.68 ± .04	.65 ± .05	.58 ± .04	.39 ± .05
P3b					
N−	135	.62 ± .05	.61 ± .05	.49 ± .04	.29 ± .05
N+	113	.29 ± .05	.29 ± .05	.24 ± .04	.12 ± .04
All Pts P3b	248	.47 ± .04	.46 ± .04	.38 ± .03	.22 ± .03
P4a					
N−	79	.50 ± .06	.45 ± .07	.44 ± .06	.23 ± .06
N+	58	.33 ± .07	.33 ± .07	.26 ± .06	.20 ± .05
All Pts P4a	137	.44 ± .05	.41 ± .05	.33 ± .04	.22 ± .04
Organ-confined†					
N−	594	.85 ± .02	.82 ± .02	.78 ± .02	.56 ± .02
N+	75	.46 ± .06	.44 ± .06	.45 ± .06	.37 ± .06
All Pts	669	.80 ± .02	.77 ± .02	.74 ± .02	.54 ± .02
Extravesical‡					
N−	214	.58 ± .04	.55 ± .04	.47 ± .04	.27 ± .04
N+	171	.30 ± .04	.30 ± .04	.25 ± .04	.17 ± .03
All Pts	385	.46 ± .03	.44 ± .03	.37 ± .03	.22 ± .03
LN− Pts	808	.78 ± .02	.75 ± .02	.69 ± .02	.49 ± .02
LN+ Pts	246	.35 ± .03	.34 ± .03	.31 ± .03	.23 ± .03
Total group	1,054	.68 ± .02	.66 ± .02	.60 ± .02	.43 ± .02

NOTE. Estimated probabilities of recurrence-free and overall survival at 5 and 10 years in 1,054 patients undergoing cystectomy, according to pathologic stage (with or without lymph node involvement) and pathologic subgroups. Probabilities of recurrence-free and overall survival are based on Kaplan-Meier estimates.[15] Plus-minus values are estimates of the SE calculated using Greenwood's formula.[16]

Abbreviations: N−, without lymph node involvement (node-negative); N+, with lymph node involvement (node-positive); Pts, patients.

*Pathologic stage is based on 1987 TNM system.[13]

†Organ confined, including Po, Pa, Pis, P1, P2, and P3a bladder tumors.

‡Extravesical, including P3b and P4 bladder tumors.

pathologic stage ($P = .17$). The 5- and 10-year recurrence-free survival for this pathologic subgroup of organ-confined lymph node negative tumors was 85% and 82%; and overall survival at 5 and 10 years was 78% and 56%, respectively (Fig 3).

The chance of remaining recurrence-free for the 214 patients (20%) with nonorgan-confined (extravesical) lymph node–negative bladder tumors (P3b, P4) was not significantly different when stratified by individual pathologic stage ($P = .10$) (Table 3). The 5- and 10-year recurrence-free and overall survival for this pathologic subgroup of extravesical, lymph node–negative tumors was 58% and 55%, and 47% and 27%, respectively (Fig 3).

Patients with lymph node–positive disease demonstrated significantly worse survival and higher recurrence rates compared with those with no lymph node involvement ($P < 0.001$). The recurrence-free and overall survival for the 246 patients (23%) with lymph node–positive disease at 5 and

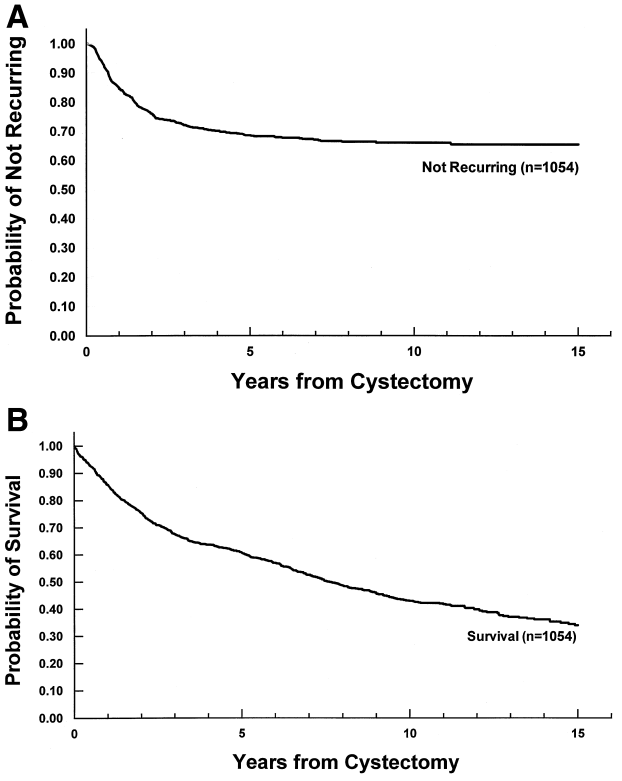

Fig 1. (A) Recurrence-free survival and (B) overall survival in 1,054 patients undergoing radical cystectomy with intent to cure for invasive bladder cancer.

10 years was 35% and 34%, and 31% and 23%, respectively (Table 3, Fig 3). Survival rates in this group of patients with lymph node positive disease could be stratified further by the primary bladder tumor (p stage) and by the total number of lymph nodes involved (Fig 4). Patients with fewer than five positive lymph nodes had significantly higher survival rates than those with five or more lymph nodes involved ($P = .003$) (Fig 4A). Similarly, patients with lymph node–positive disease and organ-confined primary bladder tumors had significantly higher survival rates than lymph node–positive patients with nonorgan confined (extravesical) primary bladder tumors ($P = .004$) (Fig 4B).

Recurrence-free and overall survival were significantly related to pathologic subgroup ($P < .001$) (Table 3, Fig 3). Patients with organ-confined lymph node–negative tumors had the lowest recurrence and highest survival rates statistically compared with patients with lymph node–positive disease, who had the highest recurrence and worst survival rate. Patients with nonorgan-confined (extravesical) lymph node–negative tumors demonstrated intermediate recurrence and survival rates.

Recurrence Site

A total of 311 patients (30%) developed a bladder cancer recurrence. Among those patients who experienced recurrence, the median time to any tumor recurrence was 12 months; 86% of recurrences occurred within 3 years, and the latest recurrence was observed at 11.1 years. Of the 311 patients with recurrences, 234 (75%) developed a distant recurrence, whereas 77 patients (25%) developed a local pelvic tumor recurrence. The median time for a distant and local recurrence was 12 and 18 months, respectively.

Local tumor recurrences could be stratified by pathologic subgroups. Patients with organ-confined and extravesical lymph node–negative tumors had local recurrence rates, in which only local disease was present at the time of first recurrence, of 6% and 13%, respectively. Those with lymph node–positive disease demonstrated only a 13% local recurrence rate after cystectomy, with only local disease present at the time of first recurrence. Distant recurrences in these same pathologic subgroups increased progressively from 13% in those with organ-confined lymph node–negative tumors to 32% in those with extravesical lymph node–negative tumors. Overall, 52% of patients with lymph node–positive tumors developed a distant recurrence.

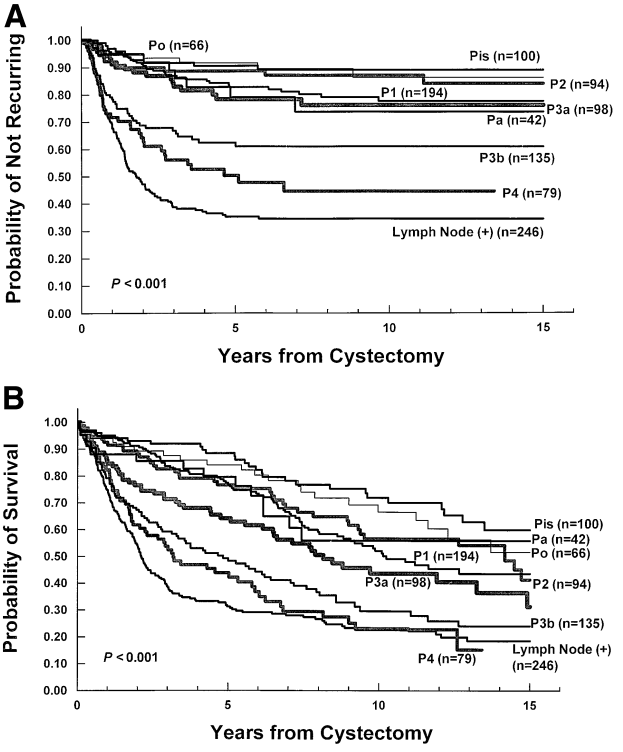

Fig 2. (A) Recurrence-free survival and (B) overall survival in 1,054 patients after radical cystectomy stratified by pathologic stage and lymph node status.

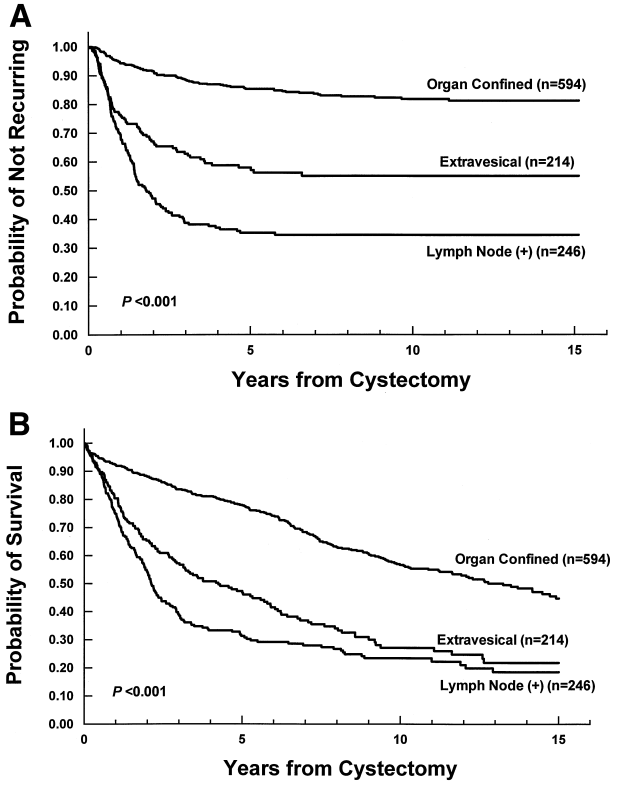

Fig 3. (A) Recurrence-free survival and (B) overall survival in 1,054 patients after radical cystectomy stratified by pathologic subgroups (organ confined, extravesical, and lymph node positive.

Impact of Additional Therapy

The impact of adjuvant chemotherapy is difficult to assess because of patient selection, but it remains a component in the treatment of patients with invasive bladder cancer. Since 1978, 255 (27%) of 960 patients received systemic chemotherapy either in an adjuvant setting based on the pathologic analysis of the cystectomy specimen and lymph nodes or in a preoperative neoadjuvant setting before surgery. Previously, we published a prospective clinical trial that demonstrated a benefit of prolonged time to recurrence for patients with P3 disease or greater who were randomized to postoperative adjuvant chemotherapy compared with a similar group.[5] Figure 5 illustrates the long-term recurrence free and overall survival curves for the 91 patients in this trial, with a median follow-up of 14 years (range, 8 to 18 years).

DISCUSSION

Invasive TCC of the bladder is generally a lethal disease requiring aggressive therapy, with fewer than 15% of TCC patients surviving 2 years if untreated.[20] The optimal goals of treatment for any invasive bladder cancer should include (1) long-term survival, (2) prevention of pelvic recurrence or development of metastatic bladder cancer, and (3) an excellent quality of life. The development of metastatic bladder cancer after local treatment failure is nearly uniformly fatal, with few durable complete responses from any form of systemic chemotherapy.

We demonstrate in a large series of patients with long-term follow-up that radical cystectomy with en bloc bilateral pelvic iliac lymphadenectomy and urinary diversion can be performed safely with excellent bladder cancer control and a low incidence of local pelvic recurrence. Furthermore, the quality of life after cystectomy has improved as lower urinary tract options have evolved into an orthotopic form of diversion; allowing most patients to store urine and void per urethra, without the need of a stoma, an ostomy appliance, or the need for catheterization.

In this series of 1,054 patients treated with radical cystectomy for invasive bladder cancer, the chance of surviving 5 years without evidence of disease is 69%, with

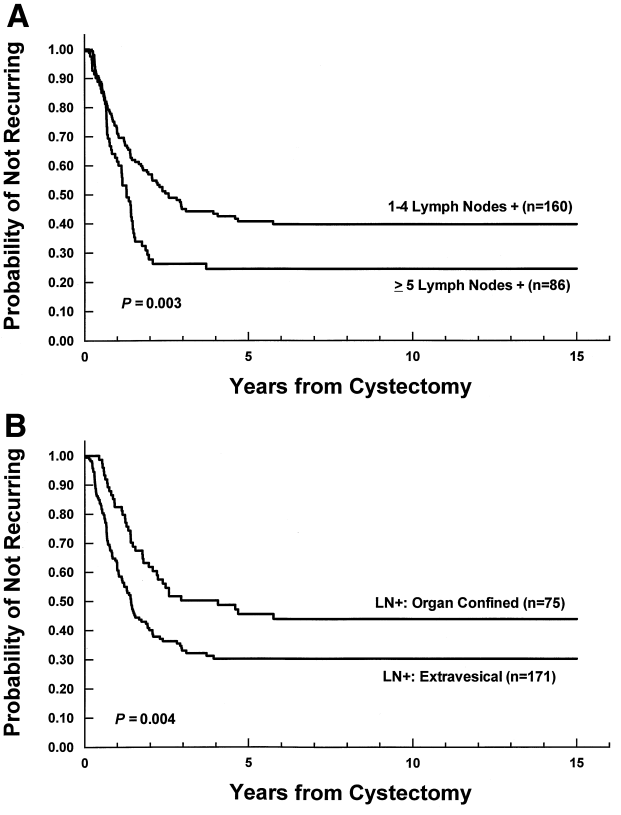

Fig 4. Recurrence-free survival in 246 patients after radical cystectomy with lymph node–positive disease stratified by (A) total number of lymph nodes involved (1-4 or ≥ 5 positive lymph nodes) and (B) stage of the primary bladder tumor (organ-confined p stage or extravesical p stage).

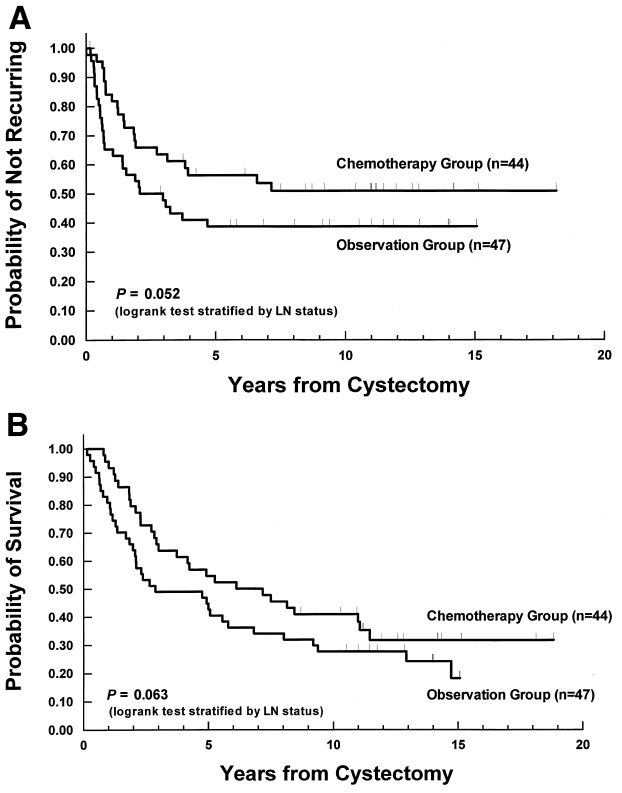

Fig 5. (A) Recurrence-free survival and (B) overall survival in 91 patients with P3, P4, or lymph node–positive disease after radical cystectomy, randomized to observation or chemotherapy.[5]

an overall survival of 60% at 5 years. Most deaths from bladder cancer occur within the first 3 years after cystectomy, after which very few patients die as a result of bladder cancer. The 5- and 10-year recurrence-free and overall survival information reported herein provide data with which other forms of therapy for invasive bladder cancer can be compared.

This study demonstrates that pathologic stage is an important survival determinant in patients undergoing cystectomy for bladder cancer. In addition, certain pathologic subgroups can be identified that stratify patients into different prognostic categories. This stratification may help dictate the need for adjuvant therapy. Of the 1,054 patients followed, 56% had pathologically organ-confined, lymph node–negative bladder tumors. The survival results in this subgroup of patients were excellent. No survival difference was observed when comparing superficially noninvasive (Pis, Pa), lamina propria invasive (P1), and muscle invasive (P2, P3a) tumors, as long as the tumor was confined to the bladder (ie, negative nodes). Collectively, the recurrence-free survival in this pathologic subgroup of organ-confined, lymph node–negative bladder tumors was 85% at 5 years, and 82% at 10 years. Similar results for superficial bladder tumors treated with cystectomy have been reported.[3,6]

Nonorgan-confined (extravesical), lymph node–negative tumors were found in approximately 20% of the patients undergoing radical cystectomy in this series. No survival difference was observed between extravesical P3b and P4 tumors. The recurrence-free survival in this pathologic subgroup of nonorgan-confined lymph node– negative tumors was 58% at 5 years, and 55% at 10 years. Patients with extravesical tumors demonstrated significantly higher recurrence rates and worse survival compared with those with organ-confined tumors ($P < .001$).

At the time of cystectomy, 23% of our patients demonstrated lymph node–positive disease. This underscores the virulent and metastatic capabilities of high-grade, invasive bladder cancer. Despite lymph node involvement, nearly 31% of these patients were alive at 5 years and 23% were alive at 10 years. It is possible that our approach, a meticulous, extended pelvic iliac lymph node dissection, may contribute to the long-term survival of many of these patients.[2,21] The impact of neoadjuvant or adjuvant therapy in this group of patients, although difficult to assess and subject to selection bias, may also play a role in the outcomes of patients with lymph node–positive disease.

The prognosis in patients with lymph node–positive disease in this study could be stratified by the number of lymph nodes involved and by the p stage of the primary bladder tumor. Patients with fewer than five positive lymph nodes had a 41% recurrence-free survival at 10 years, compared with 24% of patients with five or more lymph nodes at 10 years. Similar differences were noted when stratifying patients by p stage. Patients with lymph node–positive disease and organ-confined bladder tumors had a significant recurrence-free survival advantage (46%) compared with those with nonorgan-confined (30%) tumors at 10 years. Similar results with lymph node–positive disease after cystectomy have been reported previously.[2,3,7,21,22] Patients with any lymph node involvement, however, remain at high risk for disease recurrence and should be considered for adjuvant treatment strategies. We have analyzed the data from our series and found that the only pathologic group of patients who benefited significantly from adjuvant chemotherapy, from a recurrence-free and overall survival standpoint, was the lymph node–positive group (data not presented).

As a result of improved medical, surgical, and anesthetic techniques, the mortality and morbidity from radical cystectomy have decreased dramatically . We report a 3% mortality rate, comparable to other contemporary radical cystectomy series.[3,6,7,23] In our series, the administration of

preoperative therapy (radiation and/or chemotherapy) and the form of urinary diversion performed (continent or incontinent) did not noticeably alter the mortality. In addition, the reported early complication rate of 27% in this group of patients included all complications within the first 4 months of surgery: those related to the cystectomy, to perioperative care, and to the urinary diversion. The administration of preoperative therapy and the form of urinary diversion performed did not impact obviously on the overall complication rate. Similar results have been reported.[6] Most of these early complications after cystectomy can be appropriately managed nonoperatively, without further sequelae.[24] Strict attention to perioperative details, meticulous surgery, and a team-oriented surgical and postoperative approach are critical to minimize morbidity and mortality and to ensure the best clinical outcomes after radical cystectomy in these patients.

Radical cystectomy provides excellent local (pelvic) control for the treatment of invasive bladder cancer. An overall local pelvic recurrence rate of 9% was observed in this series. Patients with organ-confined lymph node negative tumors demonstrated only a 6% local recurrence rate, compared with a 13% local recurrence rate in those with nonorgan- confined lymph node negative tumors. Even those at highest risk of a local recurrence (lymph node–positive disease) had only a 13% local recurrence rate after cystectomy. As reported previously, use of high-dose, short-course, preoperative radiation therapy does not seem to reduce the risk of pelvic recurrence[4]; nearly all patients suffering pelvic recurrence died of their disease despite additional therapeutic efforts.

The development of orthotopic lower urinary tract reconstruction has dramatically lessened the impact of cystectomy on the quality of life of patients after removal of the bladder. Orthotopic diversion has eliminated the need for a cutaneous stoma, urostomy appliance, and the need for intermittent catheterization. Continence rates after orthotopic diversion are excellent, providing patients a more natural voiding pattern per urethra.[8,9] Currently, approximately 90% of male and female patients are considered appropriate candidates for orthotopic urinary diversion with a low risk of a urethral tumor recurrence after reconstruction.[25] The option of lower urinary tract reconstruction to the urethra has also been shown to decrease physician reluctance and increase patient acceptance to undergo earlier cystectomy for bladder cancer when the disease may be at a more curable stage.[26]

We believe the only contraindication to orthotopic urinary diversion is the presence of tumor within the urethra or extending to the urethral margin as determined by frozen section analysis of the distal surgical margin at the time of cystectomy; compromised renal function (creatinine $>$ 2.5 ng/mL); or the presence of inflammatory bowel disease. Even in patients with locally advanced disease, orthotopic diversion can be employed without concern over subsequent tumor-related reservoir complications. Whether patients have a better quality of life after cystectomy or after bladder-sparing protocols, which require significant and prolonged treatment of the bladder with the potential for tumor recurrence, has not been clarified.

Clinical staging errors in patients with invasive bladder cancer have been reported to occur in 30% to 50% of patients.[3,6,7] Unlike any other therapy, radical cystectomy pathologically stages the primary bladder tumor and regional lymph nodes. This histologic evaluation provides important prognostic information and may help identify high-risk patients who may benefit from adjuvant therapy. Our data suggest that patients with extravesical tumor extension, or with lymph node positive-disease, seem to be at increased risk for recurrence and may be considered for adjuvant treatment strategies. Additionally, the recent application of molecular markers based on pathologic staging and analysis, may also serve to identify patients at risk for tumor recurrence who may benefit from adjuvant forms of therapy.[27]

The clinical results reported from this large group of patients over an extended period of time demonstrate that radical cystectomy provides good survival results, with excellent local recurrence rates for invasive bladder cancer. Furthermore, improvements in orthotopic urinary diversion have improved the quality of life in patients after cystectomy. The results from this large series of patients provide sound data and a standard with which other forms of therapy for invasive bladder cancer can be compared.

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