

## ORIGINAL ARTICLE

# Radical Cystectomy in the Treatment of Bladder Cancer: Oncological Outcome and Survival Predictors

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**Background/Purpose:** To better understand the result of radical cystectomy in the treatment of bladder cancer, we analyzed our data and reported the oncological outcomes and survival predictors.

**Methods:** Patients underwent radical cystectomy for bladder transitional cell carcinoma between March 1995 and July 2007 were evaluated. The clinical course, pathological characteristics, and clinical outcomes were described and analyzed.

**Results:** A total of 148 patients (98 men and 50 women) with a median age of 66.7 years (range: 23.8–83.3) were included in the study. Median follow-up was 64 months. The perioperative mortality was 2.7%. The 5-year recurrence-free survival (RFS) and overall survival (OS) for all 148 patients was 61% and 53%, respectively. The 5-year RFS and OS were 68% and 62% for pT2, 65% and 59% for pT3, 11% and 9% for pT4, and 37% and 31% for nodal-positive disease, respectively. The number of positive lymph nodes was significantly associated with survival: 5-year RFS and OS were 54% and 33%, for patients with only 1–3 positive lymph nodes, whereas, all patients with  $\geq 4$  positive lymph nodes had recurrence. On multivariate analysis, age  $> 60$  years, pT4 tumors, and lymph node involvement had a negative impact on survival.

**Conclusion:** Radical cystectomy can be curative in a significant portion of patients with organ-confined (T2 or less) and extravesical (pT3) bladder cancer. Age  $> 60$  years, pT4 tumors, and nodal metastases were associated with poor prognosis. Patients with limited lymph node involvement (1–3 nodes) can be cured by surgery alone, whereas a more extensive lymph node metastasis ( $\geq 4$  nodes) eventually results in recurrence. Concomitant prostate cancer is of low grade and early stage, and is clinically insignificant. [*J Formos Med Assoc* 2009;108(11):872–878]

**Key Words:** bladder cancer, cystectomy, lymph nodes, neoplasm metastasis, survival

Bladder cancer is the second most common genitourinary malignancy, and  $> 90\%$  of all primary bladder cancer is transitional cell carcinoma (TCC). In 2005 alone, 1900 new patients were diagnosed with bladder cancer in Taiwan, and 747 patients died of the disease.<sup>1</sup> At presentation, about 70% of patients present with superficial

bladder cancer (Ta, T1, or CIS); the remainder present with or develop invasive disease (muscle-invasive, locally advanced, or metastatic disease). Radical cystectomy remains the gold standard for the treatment for muscle-invasive bladder cancer, although bladder-sparing treatment is appropriate in selected patients.

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We reviewed and analyzed retrospectively a series of patients who underwent radical cystectomy for bladder cancer over the past 10 years. The oncological outcome and survival predictors are reported in this paper.

## Patients and Methods

Between March 1995 and July 2007, a total of 162 patients with bladder cancer underwent radical cystectomy at our institute (National Taiwan University Hospital Taipei, Taiwan). Radical cystectomy referred to radical cystoprostatectomy in male patients and anterior exenteration in female patients. For all patients, standard pelvic lymph node dissection was performed. The borders of lymph node dissection were composed of the genitofemoral nerve laterally, the bladder wall medially, the endopelvic fascia caudad, the bifurcation of the common iliac artery cephalad, and the obturator fossa as the floor. All lymph nodes along with the soft tissue in the space were removed. Urinary diversion was performed with one of the following methods: ileal conduit, ileoneobladder, Indiana pouch, or percutaneous nephrostomy. The choice of urinary diversion was up to the surgeons, with consideration of the patients' condition and preference.

The pathological diagnosis of the 162 patients comprised 148 TCCs, four adenocarcinomas, two squamous cell carcinomas, and one small cell carcinoma. Data were incomplete in seven patients, who were excluded from the study. Only patients with TCC were reviewed and analyzed subsequently. The 1997 tumor-node-metastasis (TNM) classification of the American Joint Committee on Cancer was used for pathological staging,<sup>2</sup> and tumors were designated as pT0, pTis, pTa, pT1, pT2, pT3, pT4, or pN+. Superficial diseases (pTis, pTa, or pT1) were grouped together for further analysis.

Postoperatively, patients were followed periodically, usually at 3-month intervals in the first 2 years, 6-month intervals in the following 3 years, and annually thereafter. Physical examinations,

serum biochemistry tests, and urinalysis were performed at every follow-up. Radiographic evaluation, including abdominal/pelvic computed tomography and chest radiography, was performed at 3- or 6-month intervals, and at least once a year. Bone scans were performed electively when clinically indicated. Recurrence was indicated by any radiographically and/or pathologically proven recurrent tumors: they were defined as local recurrence if the mass was located in the pelvic cavity and as distant recurrence if the mass appeared elsewhere.

Time to recurrence was calculated as the time from cystectomy to the date of the first documented clinical recurrence; recurrence-free survival (RFS) was calculated as the time from cystectomy to the last follow-up if the patient had no evidence of recurrence; patients who died before recurrence were censored at the time of death. Overall survival (OS) was calculated as the time from cystectomy to the date of death. All deaths, regardless of cause, were counted as events; patients who were still alive were censored at the date of last contact. Perioperative mortality was defined as any death within 30 days of surgery or before discharge.

Kaplan-Meier plots were used to estimate the RFS and OS for the 148 TCCs classified by pathological stage. The log-rank test was used to compare subgroups of patients in terms of survival. Cox regression was used to test survival predictors in multivariate analysis. All *p* values reported were two-sided, and *p* < 0.05 was considered to indicate statistical significance. All data in the present study were analyzed with the SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

## Results

The demographic characteristics of the 148 patients with bladder TCC are shown in Table 1. Ninety-eight (66.2%) were men and 50 (33.8%) were women. The median age was 66.7 years (range: 23–83.3 years).

A total of 113 patients (76.3%) underwent radical cystectomy alone. For concomitant upper tract

**Table 1.** Demographics of 148 bladder TCC treated with radical cystectomy\*

Median age (range)	66.7 (23.8–83.3)
Sex	
Male	98 (66.2)
Female	50 (33.8)
Operation	
RC	113 (76.3)
RC + unilateral NU	14 (9.5)
RC + bilateral NU	21 (14.2)
Diversion	
Ileal conduit	82 (55.4)
Ileoneobladder	15 (10.1)
Indiana pouch	7 (4.7)
PCN	7 (4.7)
Perioperative mortality	4 (2.7)
Pathological stage	
pT0	23 (15.5)
pTis	3 (2.0)
pTa	8 (5.4)
pT1	11 (7.4)
pT2	39 (26.4)
pT3	24 (16.2)
pT4	16 (10.8)
pN+	24 (16.2)
Prostate cancer ( <i>n</i> = 11)	
Organ-confined	11
Gleason score = 7	4
Gleason score < 7	7
Nodes removed	10 (0–35)
Neoadjuvant C/T	8 (5.4)
Adjuvant C/T	1 (0.7)
Adjuvant R/T	3 (2.0)

\*Data presented as *n* (%) or mean (range). RC = radical cystectomy; NU = nephroureterectomy; PCN = percutaneous nephrostomy; C/T = chemotherapy; R/T = radiotherapy.

urothelial carcinoma, 14 (9.5%) underwent simultaneous unilateral nephroureterectomy, and 21 (14.2%) underwent bilateral nephroureterectomy. Urinary diversion was performed with ileal conduit in 82 (55.4%), ileoneobladder in 15 (10.1%), Indiana pouch in seven (4.7%), and percutaneous nephrostomy in seven (4.7%) patients. Perioperative mortality occurred in four (2.7%) patients.

Pathological staging showed that 122 (83.8%) patients had no lymph node involvement, and they comprised 23 (15.5%) patients with pT0, three (2.0%) with pTis, eight (5.4%) with pTa, 11 (7.4%) with pT1, 38 (25.7%) with pT2, 24 (16.2%) with pT3, and 16 (10.8%) with pT4 tumors. Another 24 (16.2%) patients were staged as having lymph node involvement (pN+). The median number of pelvic lymph nodes retrieved was 10 (range: 0–35). Concomitant prostate cancer was found in 11 (11.2%) of the 98 male patients. All were organ-confined (pT2). Seven (63.6%) patients had a Gleason score of ≤6, and four (36.4%) had a score of 7. During follow-up, none of these patients had evidence of prostate cancer recurrence.

The 5-year RFS and OS for all 148 patients was 61% and 53%, respectively. Table 2 and Figure 1 show the 5-year RFS and OS rates for each pathological stage. The 5-year RFS and OS for patients with only 1–3 positive lymph nodes were 54% and 33%, respectively, whereas recurrence developed in all patients with ≥4 positive lymph nodes (Table 2 and Figure 2).

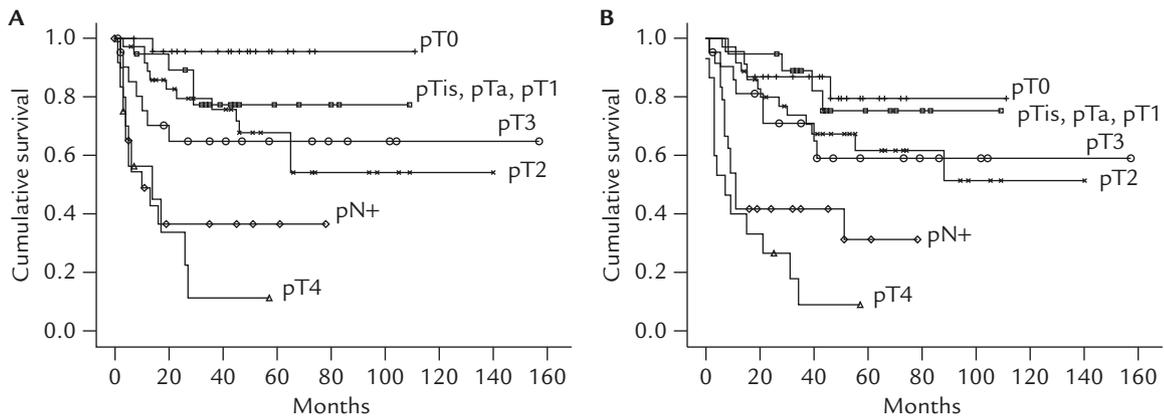
A total of 44 patients (29.7%) developed cancer recurrence. Among those who experienced recurrence, the median time to recurrence was 10.5 months. Of the 44 patients with recurrence, 16 (36.4%) had local recurrence, and 28 (63.6%) had distant recurrence. Fourteen of the 16 local recurrences developed within 2 years, with only two late local recurrences at 45 and 46 months. Twenty-two of the 28 distant recurrences developed within 2 years, with the latest recurrence at 65 months. Table 3 shows the median time to recurrence and recurrence patterns for each pathological stage. Time to recurrence and the recurrence patterns are shown in Table 3.

Table 4 shows the univariate and multivariate analysis of the impact of clinical and pathological factors on survival. In univariate analysis, age >60 years, pT4 tumors, nodal positive diseases, and a lymph node density ≥0.2 were significant. In multivariate analysis, only age >60 years, pT4 tumors, and nodal positive diseases were significant.

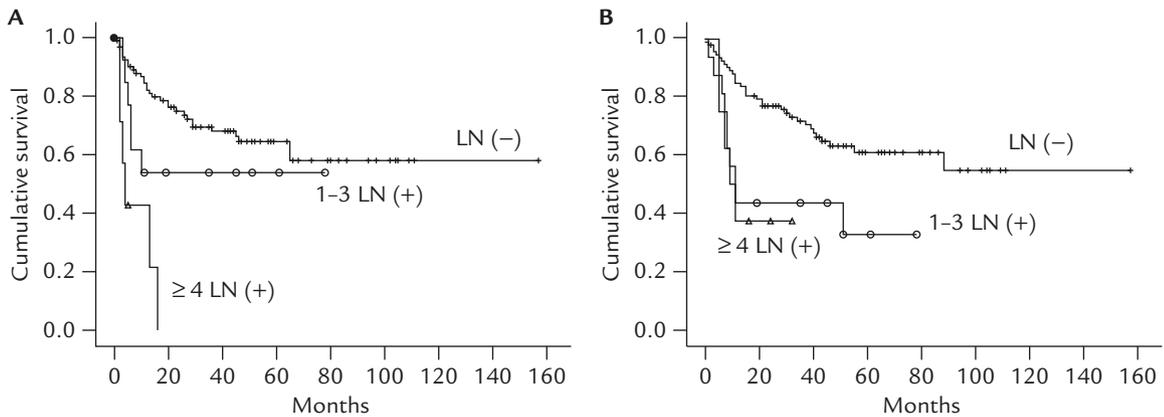
**Table 2.** The 5-year recurrence-free survival (RFS) and overall survival (OS) of 148 patients with different pathological stages after radical cystectomy\*

	<i>n</i>	5-year RFS	5-year OS
All	148	0.64 ± 0.05	0.53 ± 0.05
pT0	23	0.96 ± 0.04	0.80 ± 0.10
pTa, pT1, pTis	22	0.77 ± 0.10	0.66 ± 0.13
pT2	39	0.68 ± 0.09	0.62 ± 0.09
pT3	24	0.65 ± 0.11	0.59 ± 0.11
pT4	16	0.11 ± 0.11	0.09 ± 0.08
pN+	24	0.37 ± 0.11	0.31 ± 0.12
LN(+) (1–3 nodes)	16	0.54 ± 0.14	0.33 ± 0.13
LN(+) (≥ 4 nodes)	8	0	N/A

\*Data presented as *n* or estimated probability ± standard error. N/A = not available; LN = lymph nodes.



**Figure 1.** (A) The 5-year recurrence-free survival and (B) overall survival curves after radical cystectomy, grouped by pathological stage.



**Figure 2.** (A) The 5-year recurrence-free survival and (B) overall survival curves after radical cystectomy, grouped by the number of positive lymph nodes.

**Table 3.** Time to recurrence and recurrence patterns after radical cystectomy

Stage	Time to recurrence (mo)	Recurrence patterns (%)	
		Local	Distant
pT0	14.0	0	100.0
pTa, pT1, pTis	24.5	25.0	75.0
pT2	19.0	27.3	72.7
pT3	8.0	57.1	42.9
pT4	5.0	55.6	44.4
pN+	4.5	25.0	75.0

**Table 4.** Survival predictors of radical cystectomy for bladder cancer\*

	Univariate	<i>p</i>	Multivariate	<i>p</i>
Age > 60 (yr)	2.03 (1.11–3.71)	0.02	1.04 (1.01–1.07)	<0.01
pT4 vs. pT0–3	5.39 (3.14–9.26)	<0.01	4.38 (2.09–9.19)	<0.01
LN(+)	2.63 (1.45–4.77)	<0.01	1.92 (1.25–2.98)	0.02
> 10 lymph nodes retrieved	1.03 (0.58–1.82)	0.92	1.24 (0.68–2.28)	0.48
LN density ≥ 0.2	3.16 (1.62–6.19)	<0.01	1.71 (0.52–5.68)	0.38

\*Data presented as hazard ratio (95% confidence interval). LN = lymph nodes.

## Discussion

In the present study, we reported the oncological outcomes of radical cystectomy for bladder cancer. The 5-year RFS and OS were 68% and 62% for pT2, 65% and 59% for pT3, 11% and 9% for pT4, and 37% and 31% for node-positive disease, respectively. Compared with the contemporary series,<sup>3,4</sup> we had a similar result for pT2, a better result for pT3, and a slightly worse result for pT4 disease. The improving survival in pT3 tumors could have been attributed to wider excision of the perivesical soft tissue. On the other hand, the worse outcome in pT4 tumors might have resulted from inadequate resection of the surrounding involved organs. Meanwhile, a perioperative mortality rate of 2.7% is generally in line with that of the contemporary series. These results suggest that radical cystectomy with pelvic lymph node dissection can be curative in a significant number of patients with organ-confined (pT0–pT2) and extravesical (pT3) bladder cancer, with an acceptable mortality rate.

The majority (81.8%) of recurrences occurred within 2 years after radical cystectomy, with the latest recurrence developing at 65 months after surgery. Therefore, the follow-up schedule should be frequent in the first 2 years and extended to at least 5 years. We also analyzed the recurrence patterns of each pathological stage: more than half of the recurrence of pT3 and pT4 diseases occurred in the pelvic cavity, compared with only one quarter in organ-confined diseases (pT0–pT2). The findings imply that more radical and wider excision is required for local control of pT3 and pT4 tumors. Moreover, as advanced bladder cancer (pT3, pT4 or pN+) recurs more rapidly, a more intensive follow-up schedule might be warranted.

Neoadjuvant chemotherapy has been shown to improve survival in invasive bladder cancer.<sup>5,6</sup> A meta-analysis, including 11 trials and 3005 patients, has shown a significant benefit associated with cisplatin-based chemotherapy, equivalent to a 5% improvement in OS at 5 years; the survival benefit of 5% exists regardless of tumor

stage (pT2, pT3, or pT4).<sup>6</sup> In our series, only eight (5.4%) patients received neoadjuvant chemotherapy. Three of them achieved pT0 status in their cystectomy specimen, and two were alive and recurrence-free at 48 and 60 months. Although the result seems to be promising, with the limited case number and the nonrandomized basis, the real effect of neoadjuvant chemotherapy could not be analyzed in the present study.

Several factors have been shown to influence survival after radical cystectomy, including age, pathological T stage, nodal status, number of lymph nodes retrieved, and lymph node density.<sup>7,8</sup> These factors were analyzed in our series: age > 60 years, pT4 tumors, and positive lymph nodes were associated significantly with poor prognosis in multivariate analysis. Herr et al have demonstrated that a greater number of lymph nodes retrieved can improve survival regardless of the nodal status.<sup>9</sup> Similarly, it has been demonstrated that extending the limits of pelvic lymph node dissection can also improve survival.<sup>10,11</sup> The effect of lymph node removal could not be shown in our analysis. This might be resulted from variability among the pathologists in terms of technique and diligence in examining the specimen and searching for nodes.<sup>7</sup> The number of lymph nodes retrieved might have been underestimated if the nodes were grossly normal. Therefore, the number of lymph nodes retrieved was not precise. As a consequence, the lymph node density could not be calculated exactly.

Lymph node metastasis, even only one positive node, is thought to represent systemic disease.<sup>12</sup> Whether nodal-positive diseases can be cured with surgery alone remains controversial. Several lines of evidence have shown that radical cystectomy along with pelvic lymph node dissection can provide long-term survival, particularly for those with localized primary tumors and minimal metastatic nodal disease.<sup>13-15</sup> In our series, we found that 33% of the patients with only 1-3 positive lymph nodes could be recurrence-free and have long-term survival. On the contrary, all patients with  $\geq 4$  positive lymph nodes eventually had recurrence. Our findings generally support the

concept that patients with only limited lymph node involvement can be cured by surgery.

Concomitant prostate adenocarcinoma was found in 11.2% of the cystectomy specimens in the present study. Without a whole-mount preparation for pathological examination, it is unlikely that the rate represented the real situation. Yang et al have reported a 33% incidence of concomitant prostate cancer in cystectomy specimens in Taiwanese men;<sup>16</sup> a rate that is similar to that in the United States. Although the rate reported in our series was underestimated, our findings showed that the majority of the concomitant prostate cancer was of low grade and early stage, and was clinically insignificant, because no patients had recurrence of prostate cancer.

In conclusion, radical cystectomy provides an eradicated treatment for organ-confined (pT0-pT2) and extravesical (pT3) bladder cancer. Age > 60 years, pT4 tumors, and nodal-positive diseases are associated with poor prognosis. Patients with limited (1-3) positive lymph nodes can be cured by surgery, whereas those with  $\geq 4$  positive lymph nodes eventually have recurrence. Concomitant prostate adenocarcinoma is of low grade and early stage, and is clinically insignificant.

## References

1. Bureau of Health Promotion, Executive Yuan, Taiwan, R.O.C. Cancer Registry Annual Report, 2005. Taipei: Bureau of Health Promotion, Department of Health, Executive Yuan, Taiwan, R.O.C.
2. American Joint Committee on Cancer. *Cancer Staging Manual*, 5th ed. Philadelphia: Lippincott-Raven, 1997: 241.
3. Herr HW, Dotan Z, Donat SM, et al. Defining optimal therapy for muscle invasive bladder cancer. *J Urol* 2007; 177:437-43.
4. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001;19:666-75.
5. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet* 2003;361: 1927-34.
6. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859-66.

7. Herr HW, Faulkner JR, Grossman HB, et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. *J Clin Oncol* 2004;22:2781–9.
8. Herr HW. The concept of lymph node density: is it ready for clinical practice? *J Urol* 2007;177:1273–6.
9. Herr HW, Bochner BH, Dalbagni G, et al. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol* 2002;167:1295–8.
10. Steven K, Poulsen AL. Radical cystectomy and extended pelvic lymphadenectomy: survival of patients with lymph node metastasis above the bifurcation of the common iliac vessels treated with surgery only. *J Urol* 2007;178:1218–4.
11. Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. *J Urol* 1998;160:2015–20.
12. Daughtry JD, Susan LP, Stewart BH, et al. Ileal conduit and cystectomy: a 10-year retrospective study of ileal conduits performed in conjunction with cystectomy and with a minimum 5-year followup. *J Urol* 1977;118:556–7.
13. Lerner SP, Skinner DG, Lieskovsky G, et al. The rationale for *en bloc* pelvic lymph node dissection for bladder cancer patients with nodal metastases: long-term results. *J Urol* 1993;149:758–5.
14. Vieweg J, Whitmore WF Jr, Herr HW, et al. The role of pelvic lymphadenectomy and radical cystectomy for lymph node positive bladder cancer. The Memorial Sloan–Kettering Cancer Center experience. *Cancer* 1994;73:3020–8.
15. Vieweg J, Gschwend JE, Herr HW, et al. Pelvic lymph node dissection can be curative in patients with node positive bladder cancer. *J Urol* 1999;161:449–54.
16. Yang CR, Ou YC, Ho HC, et al. Unsuspected prostate carcinoma and prostatic intraepithelial neoplasm in Taiwanese patients undergoing cystoprostatectomy. *Mol Urol* 1999;3:33–9.