KJU
Korean Journal of Urology

www.kjurology.org
DOI:10.4111/kju.2011.52.7.446

Urological Oncology

Does Radical Cystectomy Improve Overall Survival in Octogenarians with Muscle-Invasive Bladder Cancer?

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Purpose: We compared the efficacy of radical cystectomy (RC) and non-RC treatment [transurethral resection of bladder tumor (TURB) only, partial cystectomy, or TURB followed by radiotherapy] in octogenarians with muscle-invasive bladder cancer (MIBC).

Materials and Methods: A total of 177 patients aged 80 years or more underwent TURB at our institute, and 41 patients had MIBC according to the histologic examination. Fourteen patients with lymph node or distant metastasis were excluded, and 27 patients were ultimately included. Patients were stratified by treatment modality (RC vs. non-RC), Charlson Comorbidity Index (low CCI vs. high CCI), and clinical tumor stage (organ-confined disease vs. extravesical disease). The effects of several variables on cancer-specific and overall survival were assessed.

Results: Of the 27 patients, 11 (41%) underwent RC and 16 (59%) underwent non-RC treatment. Patients in the RC group were younger and more likely to have low CCI scores. There were no significant differences in overall or cancer-specific survival in the RC and non-RC groups. Patients with clinically organ-confined disease had better survival outcomes than did those with extravesical disease. Stratification of patients by CCI indicated that overall survival was better in patients with low CCI scores (p=0.013), although cancer-specific survival was similar in the two CCI groups. Univariate and multivariate analysis indicated that clinical tumor stage and CCI were independently associated with overall survival.

Conclusions: RC in octogenarians with MIBC does not improve overall survival compared with other treatment modalities. However, clinically organ-confined disease and low CCI score were associated with better overall survival.

Key Words: *Aged; Comorbidity; Cystectomy; Urinary bladder neoplasms*

Article History:
received 27 May, 2011
accepted 20 June, 2011

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INTRODUCTION

Bladder cancer is a common malignancy that disproportionately affects the elderly. The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program estimated that most bladder carcinoma patients are 65 years or older at the time of diagnosis, and that the median age at diagnosis is 73 years [1]. In the United States, bladder cancer is the fourth leading cause of cancer-related mortality in men aged 80 years or older [2].

Bladder cancer is a heterogeneous disease. Most bladder cancers are superficial tumors, and such patients have excellent prognoses. However, patients whose bladder cancer has invaded the proper muscle have poorer prognoses, and 20% to 40% of such patients present with or develop muscle-invasive bladder cancer (MIBC). In these cases, radical cystectomy (RC) is the gold standard treatment. However, this treatment can be associated with complications and poor quality of life. Thus, several studies have examined the use of a bladder-sparing technique to manage MIBC, especially in the elderly [3-5].

Age is often a major consideration when considering treatment options for MIBC. Data from multiple small surgical series have demonstrated that selected older patients fare comparably to their younger counterparts in terms of early and late complications and perioperative outcomes [6-8]. However, other reports suggested that advanced age may be an independent predictor of adverse oncologic and overall survival outcomes [9,10].

Treatment decisions for elderly patients with MIBC remain a significant and difficult clinical challenge. Several factors such as life expectancy, natural history of the cancer, and availability of multiple treatment modalities and complications should be considered. However, no previous study has compared the impact of different treatment modalities on the overall survival of octogenarians with MIBC. Thus, in the present study, we compared the survival outcomes of octogenarians with MIBC who underwent different treatments and identified the variables associated with overall survival.

MATERIALS AND METHODS

1. Patients

From January 1991 to December 2010, a total of 177 patients aged 80 years or more underwent transurethral resection of bladder tumor (TURB) for urothelial carcinoma of the bladder at our institute. Forty-one of these patients (23.2%) had urothelial carcinoma with proper muscle invasion according to the histological examination. Fourteen of these patients had lymph node involvement or distant metastases on preoperative imaging and were excluded. Finally, 27 patients were included in our study cohort.

Eleven of these patients underwent radical cystectomy (RC) and 16 patients underwent an alternative treatment (non-RC), which was TURB only (9 patients), partial cystectomy (4 patients), or TURB followed by radiotherapy (3 patients). Each patient was informed of the advantages and disadvantages of each procedure and decided on treatment after consultation with an urologist. In the 9 patients who underwent TURB only, bladder cancer was grossly completely removed in 4 patients, and 5 patients underwent TURB for palliation. In patients with TURB followed by radiotherapy, bladder cancer was completely removed before radiotherapy. RC was performed in patients with minimal comorbidities who were aware of possible complications and was performed with same surgical procedures in all 11 patients (standard bilateral pelvic lymph node dissection with en bloc RC followed by ileal conduit). Partial cystectomy was performed if the patient had a solitary bladder tumor, and the goal was resection of the tumor and laterally at the margins to include at least 2 cm of normal-appearing mucosa. Patients who refused surgical management after TURB were treated with radiotherapy, which consisted of a standard fractionation scheme of 30 fractions of 2 Gy (total dose, 60 Gy) over 30 days. Patients with severe comorbidities who refused further management after TURB were conservatively managed after adequate consultation.

2. Clinical and pathologic evaluation

Tumor stage and grade were recorded according to the 2010 TNM system and the 1973 WHO system, respectively [11,12]. All patients underwent chest radiography, computed tomography (CT) of the abdomen and pelvis, and bone scans for tumor staging before treatment. Age, sex, clinical stage, pathologic stage, comorbid conditions, and American Society of Anesthesiologists (ASA) score were obtained from the hospital database. Comorbid conditions at the time of treatment were obtained retrospectively from the preoperative clinical records. There were no systematic changes over the study period in the methods of acquiring patient comorbidity data. Charlson Comorbidity Index (CCI) scores, in which comorbid conditions are weighted and scored, were calculated as described by Charlson [13]. All complications occurring within 90 days after initiation of treatment were identified and graded according to an established 5-grade modification of the original Clavien system [14].

3. Statistical analysis

The causes of death were obtained from medical charts and death certificates. Patients were routinely evaluated by clinical and radiographic work-ups to identify possible evidence of disease. Patient groups were compared according to treatment modality (RC group vs. non-RC group) and CCI [low (CCI=0) vs. high (CCI$\geq$1)] using Pearson's chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Quantitative data were expressed as means±standard deviations. Cancer-specific survival and overall survival were measured from the date of initiation of treatment to the date of death from bladder cancer or other causes. Kaplan-Meier survival curves were used to estimate cancer-specific survival and overall survival according to treatment modality, tumor stage, and CCI and were compared by using the log rank test. Cox regression was performed to define independent factors associated with overall survival. All statistical tests were 2-tailed, and a p-value less than 0.05 was considered significant. All statistical analyses were performed by using the SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the characteristics of our patient cohort. The mean age was 82.5 years (IQR: 81-83) and 23 patients (85.2%) were males. According to preoperative CT scans, clinically extravesical disease was suspected in 16 patients (59.3%). Patients in the RC group were younger than those in the non-RC group ($p<0.001$). There was no statistically significant difference in the CCI and ASA scores of these two groups, but the RC group tended to have lower CCI scores (p=0.079). After treatment, patients in the RC group had a longer mean hospital stay ($p<0.001$) and experienced more major complications, defined as a Clavien

grade of 3 or higher (p=0.027). There was no significant difference in these two groups in the number of patients who required readmission after treatment (p=0.696) or the duration of readmission hospital stay (p=0.610). Stratification of patients by CCI [low (CCI = 0) vs. high (CCI≥1)] indicated no significant differences between these two groups (Table 2). More patients in the low CCI group underwent RC, although this difference was not significant (p=0.079).

TABLE 1. Clinicopathologic characteristics of the study cohort according to treatment modality

	Total	RC group	Non-RC group	p-value
No. patients	27	11	16	
Mean age±SD, years	82.5±2.1	80.8±0.9	83.6±1.9	<0.001
No. gender (%)				0.455
Male	23 (85.2)	10 (90.9)	13 (81.3)	
Female	4 (14.8)	1 (9.1)	3 (18.7)	
No. CCI (%)				0.079
Low (CCI=0)	14 (51.9)	8 (72.7)	6 (37.5)	
High (CCI≥1)	13 (48.1)	3 (27.3)	10 (62.5)	
No. ASA score (%)				0.920
Low (1-2)	25 (92.6)	10 (90.9)	15 (93.8)	
High (3-4)	2 (7.4)	1 (9.1)	1 (6.2)	
No. clinical tumor stage (%)				0.710
Organ confined	11 (40.7)	5 (45.5)	6 (37.5)	
Extravesical	16 (59.3)	6 (54.5)	10 (62.5)	
No. tumor grade (%)				0.357
Grade 2	3 (11.1)	2 (18.2)	1 (6.3)	
Grade 3	24 (88.9)	9 (81.8)	15 (93.7)	
Mean durationof hospital stay ± SD, days	21±20.2	37±22.2	10±7.6	<0.001
No. postoperative complication (%) (Clavien grade 3 or greater)	6 (22.2)	5 (45.5)	1 (6.3)	0.027
No. readmission (%)	12 (44.4)	4 (36.4)	8 (50.0)	0.696
Mean duration of readmission stay ± SD, days	8.7±15.0	9.0±20.2	8.6±10.9	0.610

RC: radical cystectomy, Non-RC: non-radical cystectomy, CCI: Charlson comorbidity index, ASA: American Society of Anesthesiologists, SD: standard deviation

During the follow-up period (mean duration, 27 months), 22 patients (81.5%) died, including 4 patients (14.8%) who died from bladder cancer at a mean time of 20 months after initiation of treatment. Nine patients (81.8%) in the RC group died and 13 patients (81.3%) in the non-RC group died (p=0.684). Two patients died from disease progression in each group, 2 patients underwent RC, 1 patient underwent partial cystectomy, and 1 patient underwent TURB only. All patients who died from bladder cancer had clinically or pathologically advanced cancer (Table 3).

There were no significant differences in overall survival or cancer-specific survival between the RC and non-RC groups (overall survival, p=0.487; cancer-specific survival,

TABLE 2. Clinicopathologic characteristics of the study cohort according to the Charlson-Comorbidity Index

	Low CCI (CCI=0)	High CCI (CCI≥1)	p-value
No. patients	14	13	
Mean age±SD, years	82.4±2.4	82.5±1.9	0.550
No. gender (%)			0.673
Male	12 (85.7)	11 (84.6)	
Female	2 (14.3)	2 (15.4)	
No. ASA score (%)			0.366
Low (1-2)	13 (92.9)	12 (92.3)	
High (3-4)	1 (7.1)	1 (7.7)	
No. treatment modality (%)			0.079
RC	8 (57.1)	3 (27.3)	
Non-RC	6 (42.9)	10 (72.7)	
No. clinical tumor stage (%)			0.144
Organ confined	7 (50.0)	4 (30.8)	
Extravesical	7 (50.0)	9 (69.2)	
No. tumor grade (%)			0.529
Grade 2	2 (14.3)	1 (7.7)	
Grade 3	12 (85.7)	12 (92.3)	
Mean durationof hospital stay ± SD, days	27.8±25.3	14.4±9.7	0.185
No. postoperative complication (%) (Clavien grade 3 or greater)	6 (42.9)	4 (30.8)	0.695
No. readmission (%)	4 (28.6)	8 (61.5)	0.128
Mean duration of readmission stay ± SD, days	8.1±8.3	9.4±11.2	0.239

CCI: Charlson comorbidity index, ASA: American Society of Anesthesiologists, SD: standard deviation, RC: radical cystectomy, Non-RC: non-radical cystectomy.

TABLE 3. Characteristics of the four patients who died from bladder cancer

	Treatment modality	Age (yr)	Gender	Clinical stage	Pathologic stage	Tumor grade	Recurrence (months)	Death (months)	CCI
1	TURB	83	Male	T3N0	-	3	3.7	10.9	1
2	PC	87	Male	T2N0	T3bNX	3	14.9	20.5	0
3	RC	81	Male	T2N0	T3bN0	3	19.3	27.5	1
4	RC	80	Male	T4N0	T4aN0	3	4.5	19.4	0

TURB: transurethral resection of bladder tumor, PC: partial cystectomy, RC: radical cystectomy, CCI: Charlson comorbidity index

p=0.994). Five-year overall survival was 27.3% in the RC group and 19.4% in the non-RC group (Fig. 1). Patients with organ-confined disease had better overall survival and cancer-specific survival than did patients with extravesical disease (overall survival, p=0.001, cancer-specific survival, p=0.014). Comparison of patients with low CCI and high CCI indicated no significant difference in cancer-specific survival (p=0.146), although overall survival was better in the low CCI group (p=0.013). Univariate analysis indicated that sex, clinical tumor stage, and CCI were associated with overall survival (Table 4). Multivariate Cox regression analysis indicated that clinically organ-confined disease and low CCI were associated with better overall survival. Treatment modality was not associated with overall survival.

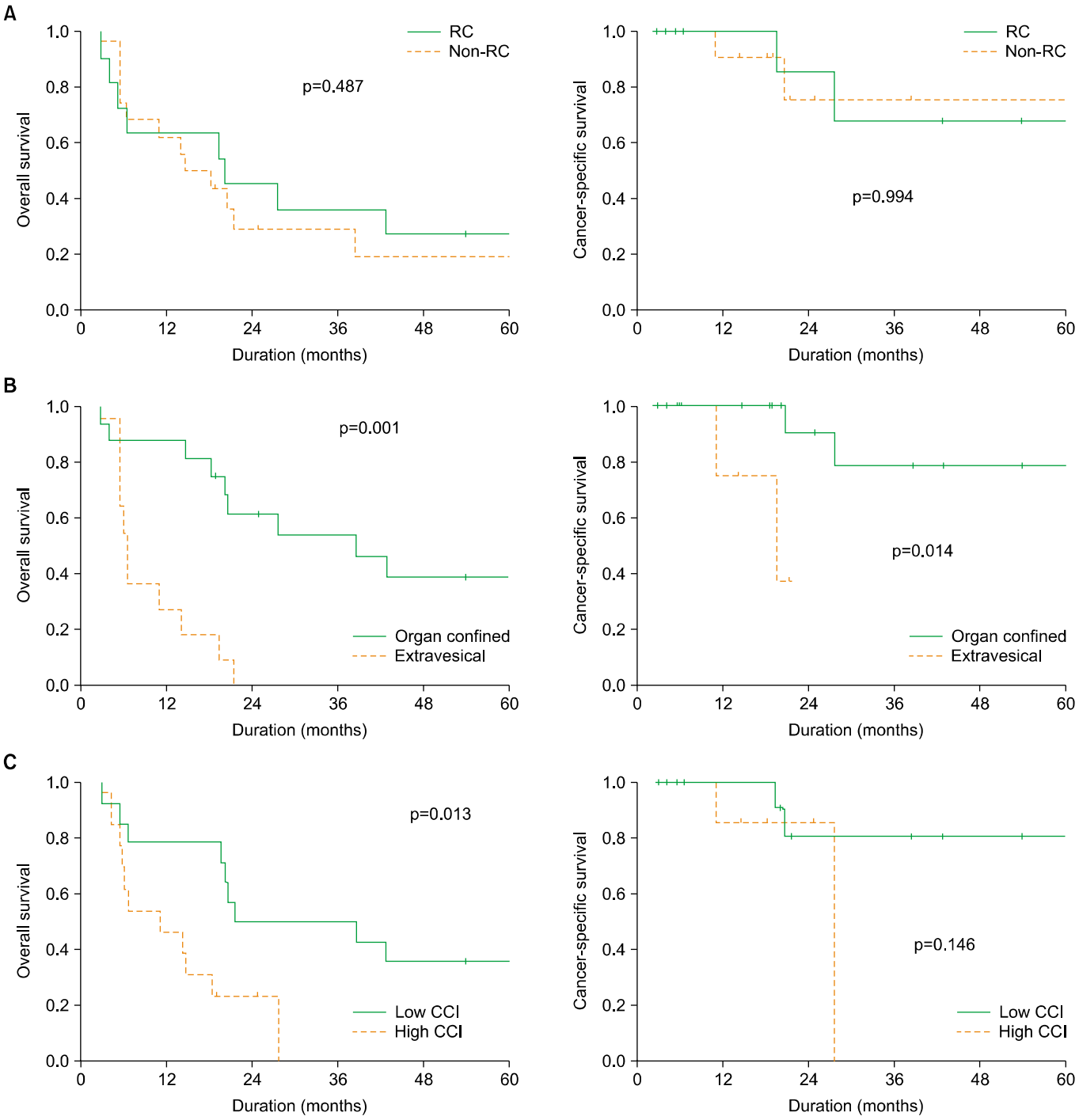

Fig. 1. (A) Overall survival (left) and cancer-specific survival (right) according to treatment modality, (B) Overall survival (left) and cancer-specific survival (right) according to tumor stage, (C) Overall survival (left) and cancer-specific survival (right) according to Charlson Comorbidity Index (CCI).

TABLE 4. Univariate and multivariate Cox regression analysis of overall survival in octogenarians with muscle-invasive bladder cancer

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Treatment modality (Non-RC vs. RC)	0.73 (0.30-1.78)	0.490	-	-
Age (continuous variable)	1.08 (0.89-1.30)	0.447	-	-
Gender (female vs. male)	5.02 (1.31-19.25)	0.019	1.27 (0.30-5.35)	0.745
CCI (high vs. low)	3.31 (1.23-8.94)	0.018	3.36 (1.08-10.44)	0.036
ASA (high vs. low)	3.54 (0.77-16.2)	0.104	-	-
Clinical tumor stage (extravesical vs organ confined)	6.45 (2.24-18.56)	0.001	6.72 (2.05-22.09)	0.002
Tumor grade (Grade 3 vs. Grade 2)	1.77 (0.40-7.86)	0.451	-	-

RC: radical cystectomy, Non-RC: non-radical cystectomy, CCI: Charlson comorbidity index, ASA: American Society of Anesthesiologists, HR: hazard ratio, CI: confidence interval.

DISCUSSION

Age is often a major consideration when weighing treatment options for elderly patients with MIBC. However, some research indicates that RC can be safely performed in elderly patients, especially in octogenarians, with acceptable mortality and morbidity [15,16]. In the current study, 1 patient (9.1%) in the RC group died within the first 90 days after radical cystectomy, similar to the mortality previously reported (0 to 18%) [17]. The incidence of major complications after radical cystectomy in the present study (45.5%) was also within the range reported in previous studies of treatment of bladder cancer patients of all ages (7.7% to 67.0%) [6-9,18-20].

In octogenarians, however, overall survival is more important than definite cancer control, because of the short life expectancy of these patients (7.8 years for males and 9.3 years for females of age 80; 5.8 years for males and 6.8 years for females of age 85) [21]. There has been no consensus about the survival benefit provided by RC in octogenarians [22,23]. In the current study, we found no significant difference in cancer-specific survival or overall survival between the RC and non-RC groups, despite the younger mean age of the RC group. Although tumor recurrence was more common in the non-RC group (p=0.051), most patients died from other causes before disease progression. Thus, we suggest that the general condition of patients be carefully evaluated before determining treatment modality for octogenarians with MIBC.

We also evaluated CCI and ASA scores to assess the conditions of the patients. When patients were stratified by CCI, those with low scores had better overall survival. This result agrees with a previous study that reported that patients with high age-adjusted CCI scores had poorer prognoses [24]. However, we found that ASA score did not provide clinically valuable information, because most patients had ASA scores of 2.

As expected, we found that tumor stage was an important predictor of survival. Although treatment modality was not associated with overall survival, CCI was associated with overall survival. Thus, CCI and tumor stage provide clinicians with valuable information in considering treatment modality. Octogenarians without comorbidities and with clinically organ-confined disease seemed to have better overall survival, whereas octogenarians with one or more comorbidities or with extravesical disease seemed to have poorer survival despite radical surgery. Thus, treatment modality should be carefully considered after assessment of tumor stage and CCI.

Patient quality of life after treatment is another important issue. In general, RC effectively reduces symptoms and relapses, and recent studies have reported improved quality of life after RC in elderly patients [8]. We evaluated the number of readmissions and the duration of the readmission stay to assess quality of life and found no significant difference between the RC and non-RC groups. Thus, the short hospital stays after treatment in the non-RC group indicates that alternative management provides comparable quality of life, as previously reported [25]. However, symptom improvements were not assessed in this study, although urinary symptoms, such as gross hematuria and dysuria are important factors for evaluating quality of life. Symptom improvements were reported as one of the greatest advantages of RC. In this regard, quality of life after RC was considered to be undervalued.

The current study was limited by its retrospective design and small number of patients. Another limitation was that three different treatment modalities were classified together as the non-RC group. Because of the small number of patients given each treatment modality, we could not evaluate the efficacy of each treatment separately. Finally, we used clinical staging instead of pathologic staging.

CONCLUSIONS

Although RC can be safely provided in selected octogenarian patients who have MIBC, RC in octogenarians with MIBC does not improve overall survival compared with other treatment modalities. Low CCI score and clinically organ-confined disease were independently associated

with better overall survival and should be considered before selecting the treatment modality for elderly patients with MIBC.

Conflicts of Interest
The authors have nothing to disclose.

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