RESEARCH COMMUNICATION

Comorbidity Relationship to Outcome of Radical Cystectomy in Chinese: a Single Institution Study with the ACE-27 Comorbidity Index

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Abstract

To determine the relationship between comorbidity and outcome after radical cystectomy in Chinese patients by using the Adult Comorbidity Evaluation (ACE)-27 index. Two-hundred-and-forty-six patients treated with radical cystectomy at the Second Xiangya Hospital of Central South University, Hunan Province, China between 2000 and 2010 were retrospectively analyzed. Medical records were reviewed for age, gender, delayed time of radical cystectomy, urinary diversion type, pelvic lymphadenectomy status, TNM stage, and pathological grade. Comorbidity information was assessed by the ACE-27 index. The outcome measurement was overall survival. Univariate and multivariate Cox proportional hazards regression analyses were used to determine the association between comorbidity and outcome. The study population consisted of 215 (87.40%) males and 31 (12.60%) females with a mean age of 62±11 years. Median duration of follow-up was 47±31 months. A total of 151 (61.38%) patents died during follow-up. Of those, 118 (47.97%) had at least one comorbidity. According to the ACE-27 scores, 128 (52.03%) patients had no comorbidity, 79 (32.11%) had mild, 33 (13.41%) had moderate, and 6 (2.45%) had severe comorbidities. Multivariate analysis indicated that moderate (p=0.002) and severe (p<0.001) comorbidity was significantly associated with decreased overall survival. In addition, age ≥70 years (p=0.002), delayed time of radical cystectomy >12 weeks (p=0.044), pelvic lymphadenectomy status (p=0.014), and TNM stage >T3 (p<0.001) were determined to be independent risk factors of overall survival. Increasing severity of comorbidity statistically correlated with decreased overall survival after radical cystectomy.

Keywords: Radical cystectomy - bladder cancer - comorbidity - ACE-27 - overall survival

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Introduction

Bladder cancer remains a worldwide health concern. In 2008, 386 000 new cases of bladder cancer were reported, and over 150 000 deaths were attributed to the disease (Jemal et al., 2011). The high rate of mortality associated with bladder cancer is believed to be linked to the advanced stage of disease upon diagnosis. For example, approximately 25% of all bladder cancers are muscle-invasive tumors at diagnosis (Nieder et al., 2008). Currently, radical cystectomy is the most effective therapy available for muscle-invasive bladder cancers and high-risk superficial cancer (Stein et al., 2001). The most recent studies on survival after radical cystectomy have recognized the potential importance of comorbidity status as a prognostic indicator. In addition, the traditional prognostic factors of bladder cancer, including age, tumor stage, and pathological grade, are also beginning to be evaluated in conjunction with comorbidity (Koppie et al., 2008; Megwalu et al., 2008; Fairey et al., 2009). However, the majority of these studies have focused on Caucasian populations, and no report to date has provided data on the impact of comorbidity in Chinese bladder cancer patients. The incidence of bladder cancer in China has increased at an alarming rate over the past decade (Parkin et al., 2005; Jemal et al., 2011). Accordingly, the number of patients undergoing radical cystectomy has also increased remarkably in the last few years. Therefore, this study was designed to investigate the prognostic effect of comorbidity on overall survival in Chinese bladder cancer patients treated with radical cystectomy. The Adult Comorbidity Evaluation-27 (ACE-27) index was chosen to assess the comorbidity status of these patients, as it was previously validated in tumor patient populations of other (non-Chinese) ethnicities. Not only were we able to determine, for the first time, the prognostic impact of comorbidity on overall survival of radical cystectomy-treated Chinese bladder cancer patients, but we also demonstrated the general utility of the ACE-27 index in this ethnic group.

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Materials and Methods

Patient characteristics and treatments

All bladder cancer patients (n=305) who had been treated with radical cystectomy in the Second Xiangya Hospital between 2000 and 2010 were retrospectively assessed. With approval from the hospital's local Ethics Committee, each patient's clinical data was collected from the medical records. Patients were excluded based upon: receipt of chemotherapy and/or radiotherapy treatments before or after radical cystectomy (n=13), incomplete clinical or pathological information (n=16), and tumor histology that was not transitional cell carcinoma (n=30). Finally, the entire study cohort consisted of 246 patients.

All patients had undergone at least one transurethral resection of bladder tumor or partial bladder resection prior to the radical cystectomy treatment. For each patient, the radical cystectomy surgical procedure included excision of the bladder, standard or limited pelvic lymphadenectomy (Hurle and Naspro, 2010; Brunocilla et al., 2011), and urinary diversion. The boundaries of the standard pelvic lymphadenectomy included common iliac bifurcation, circumflex caudal iliac vein, lymph node of Cloquet, hypogastric vessels, obturator fossa, and the genitofemoral nerve. However, limited pelvic lymphadenectomy only involved removal of the lymph nodes in the obturator fossa and external iliac vein.

Data collection

Data collected from the patient's medical records included age, gender, delayed time of radical cystectomy, urinary diversion type, pelvic lymphadenectomy status, pathological data, and comorbidity status. The delayed time of radical cystectomy was defined in our study as the duration from the day when the patient was diagnosed with muscle-invasive bladder cancer, or high-risk superficial cancer, to the date the radical cystectomy was performed. The patients were further stratified into three groups of delayed time of radical cystectomy: <8 weeks; 8-11 weeks; >12 weeks (Gore et al., 2009). The collected pathological data included tumor histology, TNM stage, and pathological grade. TNM stage was determined in accordance with the staging system published by the Union for International Cancer Control (UICC) (Sobin and Witteking, 2002). The pathological grade was evaluated by using the World Health Organization classification system (Epstein et al., 1998).

In our study, comorbidities were defined as any disease that coexisted with bladder cancer at the time of radical cystectomy (Hall, 2006). The comorbidity status was evaluated by using the ACE-27 index, which is a 27-item comorbidity tool that has been validated on adult oncology patients (Piccirillo et al., 2004). ACE-27 scores indicated comorbidity severity: 0=none; 1=mild; 2=moderate; and 3=severe. The overall comorbidity score was defined according to the highest ranked single comorbidity. In the case of two or more moderate comorbidities existing in different organ systems, the patient was scored as 'severe'. The ACE-27 index table is publically available at: http://www.rtog.org/LinkClick.aspx?fileticket=xMGEfaLHRuM%3D&tabid=290.

Follow-up

Follow-up after radical cystectomy was carried out for all 246 patients by telephoning the patient or their physicians. The zero time point for each patient was defined as the day of radical cystectomy. The end point for follow-up was either the study end point (December 30th, 2010) or patient death.

Statistical analysis

Descriptive statistics were used to assess the clinical and pathological characteristics. Univariate and multivariate Cox proportional hazards regression analyses were used to access the risk factors of overall survival. Variables having a p-value less than 0.1 in univariate analysis were applied to subsequent multivariate analysis. The Kaplan-Meier method (log-rank test) was used to estimate overall survival. All data analyses were performed with the SPSS statistical software package for Windows (version 19.0; SPSS Inc., Chicago, IL, USA), and a two-tailed p-value less than 0.05 was considered statistically significant.

Results and Discussion

Demographic, clinical, and pathological characteristics

The demographic characteristics of the 246 bladder cancer patients treated with radical cystectomy are shown in Table 1. This population was composed of 215 (87.40%) males and 31 (12.60%) females, with a mean age of 62 years. The median duration of follow-up was 47 months. One-hundred-and-fifty-one (61.38%) patients died during follow-up. A total of 118 (47.97%) patients had at least one comorbid condition. As stratified by ACE-27 score, 128 (52.03%) patients had no comorbidity, 79 (32.11%) had mild comorbidity, 33 (13.41%) had moderate comorbidity, and six had (2.45%) severe comorbidity.

Table 1. Characteristics of the Study Cohort

Variable	Category	No. of all patients (%)	No. of deaths (%)
Age	<60	99 (40.24)	54 (54.55)
	60-69	86 (34.96)	53 (61.63)
	≥70	61 (24.80)	45 (73.77)
Gender	Male	215 (87.40)	127 (59.07)
	Female	31 (12.60)	25 (80.65)
Delayed time, weeks	<8	131 (53.26)	74 (56.49)
	8-11	92 (37.40)	57 (61.96)
	≥12	23 (9.34)	21 (91.30)
Diversion type	Orthotopic	97 (39.43)	50 (51.55)
	Ileal conduit cutaneous	111 (45.12)	72 (64.86)
	Cutaneous ureterostomy	38 (15.45)	30 (78.95)
Pelvic lymph-adenectomy	Standard	134 (54.47)	72 (53.73)
	Limited	112 (45.53)	80 (71.43)
TNM stage	≤T2	127 (51.63)	70 (55.11)
	T3	91 (36.99)	61 (67.03)
	T4	28 (11.38)	27 (96.43)
Pathological grade	G1	29 (11.79)	12 (41.38)
	G2	125 (50.81)	76 (60.80)
	G3	92 (37.40)	64 (69.57)
ACE-27 comorbidity (score)	None (0)	128 (52.03)	69 (53.91)
	Mild (1)	79 (32.11)	54 (68.35)
	Moderate (2)	33 (13.41)	24 (72.73)
	Severe (3)	6 (2.45)	5 (83.33)

Table 2. Univariate Analysis of Variables Associated with Overall Survival

Variable	Hazard ratio	95% CI*	p-value
Age			
<60	1.0 (reference)		
60-69	1.460	0.996-2.139	0.052
≥70	3.407	2.271-5.112	<0.001
Delayed time, weeks			
<8	1.0 (reference)		
8-11	1.107	0.782-1.567	0.566
≥12	2.100	1.289-3.421	0.003
Diversion type			
Orthotopic	1.0 (reference)		
Ileal conduit cutaneous	1.754	1.218-2.525	0.003
Cutaneous ureterostomy	2.839	1.796-4.487	<0.001
Pelvic lymphadenectomy			
Limited	1.0 (reference)		
Standard	0.492	0.356-0.679	<0.001
TNM stage			
≤T2	1.0 (reference)		
T3	1.952	1.367-2.787	<0.001
T4	5.006	3.170-7.905	<0.001
Pathological grade			
G1	1.0 (reference)		
G2	1.715	0.932-3.156	0.083
G3	2.175	1.172-4.037	0.014
ACE-27 comorbidity (score)			
None (0)	1.0 (reference)		
Mild (1)	1.629	1.138-2.330	0.008
Moderate (2)	3.076	1.926-4.911	<0.001
Severe (3)	8.168	2.903-22.978	<0.001

*CI, confidence interval

Table 3. Multivariate Analysis of Variables Associated with Overall Survival

Variable	Hazard ratio	95% CI*	p-value
Age			
<60	1.0 (reference)		
60-69	1.180	0.748-1.860	0.447
≥70	2.217	1.327-3.706	0.002
Delayed time, weeks			
<8	1.0 (reference)		
8-11	1.032	0.722-1.474	0.862
≥12	1.681	1.014-2.785	0.044
Diversion type			
Orthotopic	1.0 (reference)		
Ileal conduit cutaneous	1.186	0.787-1.788	0.415
Cutaneous ureterostomy	1.603	0.937-2.742	0.085
Pelvic lymphadenectomy			
Limited	1.0 (reference)		
Standard	0.623	0.428-0.909	0.014
TNM stage			
≤T2	1.0 (reference)		
T3	1.391	0.944-2.051	0.095
T4	5.408	3.315-8.825	<0.001
Pathological grade			
G1	1.0 (reference)		
G2	1.187	0.633-2.223	0.593
G3	1.610	0.852-3.043	0.143
ACE-27 comorbidity (score)			
None (0)	1.0 (reference)		
Mild (1)	1.233	0.833-1.823	0.295
Moderate (2)	2.217	1.341-3.663	0.002
Severe (3)	10.431	3.735-29.136	<0.001

*CI, confidence interval

Only 23 (9.34%) patients experienced delays of >12 weeks before radical cystectomy treatment. Urinary diversions involved an orthotopic neobladder in 97 (39.43%) patients, an ileal conduit in 111 (45.12%) patients, and a cutaneous ureterostomy in 38 (15.45%) patients. The standard pelvic lymphadenectomy was performed in 134 (54.47%) patients, with the remaining 112 (45.53%) patients receiving a limited pelvic lymphadenectomy.

All resected tumors were diagnosed as transitional cell carcinoma by histological findings. UICC TNM staging indicated that 127 (51.63%) patients were ≤T2, 91 (36.99%) patients were T3, and 28 (11.38) patients were T4. Pathological findings indicated that 29 (11.79%) patients had grade 1 tumors, 125 (50.81%) had grade 2 tumors, and 92 (37.40%) had grade 3 tumors.

Univariate and multivariate Cox proportional hazards regression analyses

Univariate and multivariate Cox proportional hazard regression analyses of the entire cohort are presented in Tables 2 and 3, respectively.

Univariate Cox proportional hazard regression analysis indicated that increases in the following factors correlated with decreased overall survival: severity of comorbidity (mild, p=0.008; moderate, p<0.001; severe, p<0.001); age ≥70-years-old (p<0.001); delayed time >12 weeks (p=0.003); and urinary diversion type (p<0.001). In contrast, the standard pelvic lymphadenectomy (p<0.001) correlated with improved overall survival. Finally, TNM stage >T2 (p<0.001) and pathological grade >G2 (p=0.014) were determined to be prognostic indicators of poor overall survival.

Multivariate Cox proportional hazard regression analysis indicated that increased comorbidity was an independent risk factor of overall survival (moderate, p=0.002; severe, p<0.001). In addition, age ≥70-years-old (p=0.002), delayed time >12 weeks (p=0.044), and TNM stage >T3 (p<0.001) retained their statistical significance for association with decreased overall survival. The standard pelvic lymphadenectomy procedure (p=0.014) also remained significantly associated with increased overall survival rates. However, the association of urinary diversion type (p>0.05) and pathological grade (p>0.05) with overall survival lost statistical significance in the multivariate analysis.

Estimated overall survival stratified by comorbidity

Figure 1 shows the Kaplan-Meier estimates for overall survival stratified by comorbidity. Patients with no/mild comorbidity had a higher survival rate than patients with moderate or severe comorbidity (log-rank test p<0.001). The predicted 5-year overall survival rate for patients with no and mild comorbidity was 48.3% and 38.1%, respectively, but was only 24.8% for those with moderate comorbidity. Only six patients in our study cohort suffered from severe comorbidity, according to the ACE-27 score. One of these patients was lost to follow-up, but the remaining five died within two years of receiving the radical cystectomy procedure. Since the severe

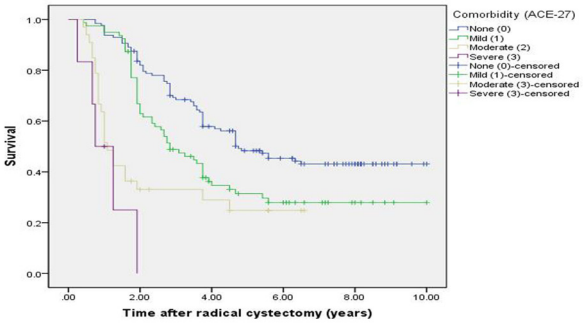

Figure 1. Kaplan-Meier Estimate of Overall Survival Stratified by ACE-27 Comorbidity Score. The log-rank test was used to assess statistical significance (p<0.001)

comorbidity group was so small, we could not estimate the corresponding 5-year overall survival rate.

Comment

Comorbidities are generally recognized as important prognostic factors for various cancers. The presence of a comorbid condition may not only mask clinical signs of cancer and delay diagnosis, but may also preclude treatment options and even complicate the established cancer and/or effects of treatment (Piccirillo and Feinstein, 1996; Extermann, 2000; Prout et al., 2005; Hall, 2006). Several studies have found that bladder cancer is strongly associated with advanced age and tobacco smoking, each of which is associated with a distinct subset of additional comorbidities (Bjerregaard et al., 2006; Fisher et al., 2009). In addition, studies of European and North American populations have shown that the comorbid condition in bladder cancer is correlated to decreased overall survival after radical cystectomy (Megwalu et al., 2008; Fairey et al., 2009; Koppie et al., 2009; Lund et al., 2010). To the best of our knowledge, no study to date has reported on the association between comorbidity and overall survival after radical cystectomy in a Chinese population. Thus, this study was designed to evaluate a Chinese bladder cancer patient population and determine the impact of comorbidity, along with other clinical and pathological factors, on the outcome of radical cystectomy.

Our multivariate analysis findings revealed that comorbidity is an independent prognostic factor of overall survival in the Chinese bladder cancer patient population. Compared to patients with no or mild comorbidity, overall survival was decreased in patients with moderate and severe comorbidity. This finding was consistent with other studies of bladder cancer patients of other ethnicities. For example, Megwalu et al. (2008) evaluated 210 patients treated with radical cystectomy and found that increased comorbidity was an independent predictor of overall survival after correction for age, AJCC stage, histological grade, and race. In another study by Fairey et al. (2009) increased comorbidity was independently associated with decreased overall survival in 468 patients treated with radical cystectomy after controlling for age, adjuvant chemotherapy, surgery procedure, tumor volume, pathological T stage, pathological lymph node status, total number of lymph nodes removed, surgical margin status, and lymphovascular invasion. Taken together with our findings, these results suggest that the radical cystectomy treatment option should be considered with respect to patient's pathological status and the presence of comorbidity. The particular comorbidity should be carefully evaluated before radical cystectomy is performed, so that appropriate pre- and post-operative management of comorbidity can be implemented to help the patient better tolerate such an aggressive operation and increase the rates of long-term survival.

The predicted 5-year overall survival rate for each comorbidity-stratified group in our study was lower than those in previously published studies. One possible explanation for this apparent discrepancy is that only 134 (54.47%) patients in our study underwent standard pelvic lymphadenectomy. It is known that the range of pelvic lymphadenectomy is closely related to the therapeutic effect of this procedure (Brunocilla and Hurle, 2010; Naspro et al., 2011). Moreover, the range of pelvic lymphadenectomy can be affected by the patient's particular anatomic structure or anatomical changes caused by repeated pelvic surgery or by anesthesia intolerance caused by cardiovascular and/or pulmonary disease, as well as by the surgeons' technical expertise. Nevertheless, the statistical results from our study demonstrated that comorbidity is independently associated with decreased overall survival.

Another finding in our study was that overall survival decreased when radical cystectomy was delayed by more than 12 weeks. Patients with delay of treatment >12 weeks experienced a 1.681-fold higher risk of death than patients delayed <12 weeks. In a similar study, Miller et al. (2003) found that comorbidity was associated with surgical delay, but did not find any correlation between comorbidity and overall survival. In our study cohort, delayed time to radical cystectomy was an independent risk factor of overall survival. However, the principal reason for delay to treatment in our institute was extra time spent in controlling comorbidities so that the patients could tolerate the radical cystectomy procedure. The second most frequent reason for delay to treatment was that many patients were reluctant to consent to surgery due to changes in voiding caused by urinary diversion. Finally, there are only a few hospitals in the Hunan Province of China (where our institute is located) that have high-volumes of patients or are affiliated with an academic institute and are capable of carrying out such a complex operation as the radical cystectomy. Thus, it is very likely that hospital scheduling complications may have delayed the time to radical cystectomy for some patients.

Other variables, such as age, pathological stage, and tumor grade were also found to correlate to decreased overall survival after radical cystectomy in our study. In contrast, receipt of the pelvic lymphadenectomy procedure was associated with increased overall survival. These findings agree with those from other similar previously published studies (Shariat et al., 2003; Madersbacher et al., 2006). However, in our study, multivariate analysis indicated that the pathological grade was not an independent impact factor of overall survival. One possible reason for this loss of statistical correlation was that the majority of our patients' pathological grade was G2 (50.81%); thus, the difference between the three groups

may not have been masked by the large bias towards one grade. In this study, as well, the urinary diversion types had no effect on overall survival by multivariate analysis, indicating that the choice of urinary diversion type could be based on both the patient's physical condition and the patient's or surgeon's preference.

Many instruments are currently available for estimating preoperative comorbidity status (Extermann, 2000; Hall, 2006). The ACE-27 index, used in our study, evolved from the Kaplan–Feinstein index, and is generally considered a reliable and valid tool for assessing comorbidity in cancer patients. However, to our knowledge, this study represents the first report of the ACE-27 index used to evaluate comorbidity in a set of Chinese bladder cancer patients. All patient information required for the ACE-27 index was able to be retrospectively obtained from the medical records of our hospital. Although, it should be noted here that the ACE-27 index has yet to be formally validated in Chinese cancer patients. It is well-recognized that many diseases differ in presentation and incidence between Chinese and Caucasian populations. Thus, future studies with larger and more clinically heterogeneous Chinese cohorts are necessary to validate the ACE-27 tool, and identify ethnic-specific improvements to strengthen its utility for particular populations.

The main limitations of our research study were the relatively small amount of patients analyzed, and the fact that they were all based in a single center. In particular, only six of our patients suffered from severe comorbidity, and five of those died within two years after receiving the radical cystectomy. Therefore, we could not calculate the estimated 5-year survival rate for this group. In addition, we did not investigate the relationship between comorbidity and tumor-specific survival because we did not have access to this information. Nonetheless, we were sufficiently powered to assess the overall survival in this patient population and provide novel insights that may help guide future clinical treatment of Chinese bladder cancer patients.

In conclusions, comorbidity was an independent prognostic factor for Chinese bladder cancer patients treated with radical cystectomy. Moreover, patients with moderate or severe comorbidity had lower overall survival after radical cystectomy than patients with no or mild comorbidity. We recommend that comorbidity status be carefully evaluated before radical cystectomy so that appropriate stabilizing interventions may be initiated prior to surgery, thereby improving survival.

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