Age, tumour stage, and preoperative serum albumin level are independent predictors of mortality after radical cystectomy for treatment of bladder cancer in Hong Kong Chinese

CME

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Objectives To evaluate the association between patient age, other clinical factors and mortality following radical cystectomy for treatment of bladder cancer.

Design Historical cohort study.

Setting A urology unit in Hong Kong.

Patients The outcomes of 117 patients who had radical cystectomies performed in one urological unit from 2003 to 2011 were reviewed. Demographic and perioperative data, including tumour stage, Charlson Comorbidity Index, and preoperative serum albumin levels were retrieved from computerised medical records. Risk factors for 30-day mortality, and cancer-specific, other-cause, and overall death rates at 5 years were calculated. The data were subsequently stratified and analysed according to age.

Results Of the 117 patients, 83 (71%) were aged 75 years or below. The mean follow-up duration was 31 (standard deviation, 29) months. Age, tumour stage, and preoperative serum albumin level, but not the Charlson Comorbidity Index, were found to be predictors of survival following radical cystectomy. The overall 30-day mortality rate was 3% in the full sample, 1% in patients aged 75 years or below, and 10% in patients aged over 75 years. There was no significant difference in 5-year cancer-caused mortalities between patients aged 75 years or below and those aged over 75 years (33% vs 33%, P=0.956). In patients older than 75 years, the 5-year other-cause and overall mortality rates were 47% and 80%, respectively; such rates were higher than those for younger patients (13% and 46%, respectively).

Conclusion Age, tumour stage, and preoperative serum albumin level were predictors of survival after radical cystectomy. Non-cancer–related death played a crucial role in the overall mortality rate in elderly patients having radical cystectomy for bladder cancer.

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New knowledge added by this study

- This is the first study on a Chinese population to investigate the association of preoperative parameters with outcomes in patients having radical cystectomy.

Implications for clinical practice or policy

- This knowledge will be important to both local patients and surgeons, whenever radical cystectomy to treat bladder cancer is being considered.

Introduction

Bladder cancer is one of the most common genitourinary tract malignancies and is primarily a disease of the elderly. The median age at diagnosis is 69 years for men and 71 years for women.[1] Radical cystectomy with bilateral pelvic lymph node dissection remains the standard treatment for patients with muscle-invasive bladder cancer (MIBC) and provides the best survival outcomes.[2] However, such surgery is associated with major morbidity and mortality. The early postoperative complication rate ranges from 25 to 57%[3,4] and early

mortality rate is about 3%,[5] and is even higher in elderly patients.[6]

Mean life expectancy is increasing in Hong Kong and many other countries. According to a survey by the United Nations, the life expectancies at birth for males and females in Hong Kong are 79 and 85 years, respectively, and are the second highest in the world after Japan.[7] A rising trend in the incidence of bladder cancer and an increase in the number of elderly patients living with bladder cancer is therefore to be expected. Treatment of MIBC in elderly patients remains a challenge. Moreover, the actual benefits of radical cystectomy in elderly patients, in terms of oncological control and perioperative mortality, remain questionable. Instruments for risk stratification and outcome prediction have been developed.[8] In the current study, we retrospectively reviewed clinical outcomes in patients with bladder cancer treated by radical cystectomies, with particular attention to any differences in postoperative mortality rates for younger and older patients.

Methods

We retrospectively reviewed the clinical and pathological data of patients who were treated by radical cystectomy for bladder cancer between May 2003 and March 2011 in a single urology unit. Preoperative evaluation included transurethral resection (TUR) of the bladder tumour and computed tomography. All grades and stages were reported according to the World Health Organization/International Society of Urologic Pathology (1998) classification and the 2002 American Joint Committee on Cancer guidelines, respectively. Open, laparoscopic, or robot-assisted cystectomies were performed according to surgeons' preferences. Patient demographic data, pre-morbid status, tumour parameters, perioperative outcomes, and survival data were retrieved from computerised clinical records. The Charlson Comorbidity Index (CCI) was used to classify co-morbid conditions before radical cystectomy. Patients were further stratified according to age into groups of ≤75 years and >75 years. The 30-day, 5-year cancer-specific, other-cause, and overall mortalities were calculated and analysed.

Continuous variables were expressed as means (± standard deviations [SDs]), and compared using Student's *t* tests. The χ^2 test was used to compare categorical variables. The 30-day mortality, cancer-specific, other-cause, and overall mortality rates at 5 years in different age-groups were compared using the Kaplan-Meier method with the log-rank statistic and the competing risk analysis[9] using R software.[10] A Cox regression model was used to identify the predictors of mortality. Subjects' survival data were checked, and no loss to follow-up was noted; every censored case was surviving on 30 September 2011.

年齡、腫瘤分期和術前血清白蛋白水平是接受根治性膀胱切除的香港華籍患者術後死亡的獨立預測因子

目的 評估病人年齡和其他臨床因素與根治性膀胱切除後死亡率之間的關係。

設計 歷史隊列研究。

安排 香港一所泌尿外科部。

患者 本研究回顧一所泌尿外科部門於2003至2011年期間進行根治性膀胱切除的117例的結果。收集人口學資料和從電腦醫療紀錄中取得的圍手術期數據，包括腫瘤分期、察爾森合併症指數和術前血清白蛋白水平。然後計算30天死亡率，以及癌症特異性、其他原因和整體五年死亡率的風險，並把數據按年齡作分層分析。

結果 117例中，83名（71%）病人的年齡為75歲或以下。平均隨訪時間31個月（標準差29個月）。年齡、腫瘤分期和術前血清白蛋白水平均為根治性膀胱切除後的存活預測因素，但不包括察爾森合併症指數。所有病人的30天死亡率為3%；年齡75歲或以下的為1%，75歲以上的則為10%。當比較年齡為75歲或以下以及75歲以上的患者，兩組因癌症死亡的五年死亡率並無顯著差異（33%比33%，P=0.956）。75歲以上的患者由於其他原因死亡的五年死亡率為47%，而五年總體死亡率為80%；死亡率均高於年輕患者（分別為13%和46%）。

結論 年齡、腫瘤分期和術前血清白蛋白水平均為根治性膀胱切除後的存活預測因子。對於接受根治性膀胱切除的膀胱癌老年患者來說，非癌症相關死亡對於總體死亡率起至關重要的作用。

Univariate Cox regressions were performed on age at surgery, gender, preoperative serum albumin level, pathological grade, tumour stage, CCI, and surgical approaches (open vs laparoscopic/robot-assisted). Factors with P values of <0.2 found in the univariate analysis were then put into the backward likelihood ratio test in the Cox regression to perform the multivariate analysis. All P values of <0.05 were regarded as statistically significant. Statistical analysis was performed with the Statistical Package for the Social Sciences (Windows version 18.0; SPSS Inc, Chicago [IL], US) and R version (2.12.2).

Results

Demographics

A total of 117 radical cystectomies were performed between 2003 and 2011, of which 99 (85%) were in males. The mean age of the overall sample was 68 (range, 43-89) years. There was no lost of follow-up during the study period and the mean (± SD)

TABLE 1. Patient demographics and clinico-pathological characteristics

Demographics/characteristics*	No. (%) of patients or mean ± standard deviation†			P value
	Overall	Age ≤75 years	Age >75 years	
No. of patients	117 (100)	83 (71)	34 (29)	-
Mean age (years)	68 ± 10	64 ± 9	80 ± 4	-
Gender				
Male	99 (85)	72 (87)	27 (79)	0.318
Female	18 (15)	11 (13)	7 (21)	
Cystectomy				
Open	71 (61)	52 (63)	19 (56)	0.496
Laparoscopic/robotic-assisted	46 (39)	31 (37)	15 (44)	
Urinary diversion				
Ileal conduit	96 (82)	62 (75)	34 (100)	0.001
Neo-bladder/continence diversion	21 (18)	21 (25)	0	
Hospital stay duration (months)				
Mean	22 ± 17	23 ± 18	22 ± 15	0.747
Median (interquartile range)	18	17 (14-26)	18 (12-24)	
Preoperative serum albumin level (g/L)	38 ± 6	39 ± 6	36 ± 7	0.007
CCI				
0	77 (66)	60 (72)	17 (50)	0.043
1-2	38 (32)	22 (27)	16 (47)	
≥3	2 (2)	1 (1)	1 (3)	
Tumour grade				
G0	5 (4)	5 (6)	0	0.328
G2	24 (21)	17 (20)	7 (21)	
G3	69 (59)	48 (58)	21 (62)	
CIS	4 (3)	4 (5)	0	
N/A	15 (13)	9 (11)	6 (18)	
Tumour stage				
NMIBC	34 (29)	25 (30)	9 (26)	0.574
T0	11	6	5	
Tis	7	7	0	
Ta	4	3	1	
T1	12	9	3	
MIBC	82 (70)	57 (69)	25 (74)	
T2	32	23	9	
T3	32	23	9	
T4	18	11	7	
N/A	1 (1)	1 (1)	0	
Lymph node				
N0	88 (75)	65 (78)	23 (68)	0.306
N1	6 (5)	5 (6)	1 (3)	
N2	14 (12)	8 (10)	6 (18)	
N3	1 (1)	0	1 (3)	
N/A	8 (7)	5 (6)	3 (9)	
Follow-up (months)				
Mean	31 ± 29	34 ± 31	24 ± 23	0.805
Range	(0-100)	(0-100)	(0-77)	

* CCI denotes Charlson Comorbidity Index, CIS carcinoma in situ, N/A not applicable, NMIBC non–muscle-invasive bladder cancer, and MIBC muscle-invasive bladder cancer
† Unless otherwise stated

follow-up duration was 31 ± 29 months. The 30-day mortality as well as 5-year cancer-specific, other-cause, and overall mortality rates were 3%, 33%, 22%, and 55%, respectively. Open radical cystectomy was performed in 71 patients and laparoscopic/robotic-assisted approaches were used in 46. In all, 96 patients underwent ileal conduit diversions and 21 received ileo-cystoplasty or continence diversion. The clinico-pathological variables are summarised in Table 1.

Age, Charlson Comorbidity Index, tumour stage, and preoperative serum albumin level

Of the 117 patients, 83 (71%) were aged ≤75 years and 34 (29%) were aged >75 years. The CCI for 98% of the overall sample was 0 or 1-2 (66% and 32%, respectively). In all, 62 (53%) of the patients had preoperative serum albumin levels of ≤39 g/L and 55 (47%) had higher levels. Overall, 29%, 27%, 27% and 15% of the patients had T1, T2, T3 and T4 bladder cancers, respectively. There were 18 patients (15%) with lymph node metastasis.

Univariate analysis identified age at surgery, tumour stage, preoperative serum albumin level, and pathological grade as independent predictors of overall mortality at 5 years post–radical cystectomy. The multivariate analysis indicated that younger age at surgery, lower tumour stage, and a higher preoperative serum albumin level were significantly associated with improved overall survival (Table 2).

Cancer-specific, other-cause, and overall mortalities according to age

The data were further analysed according to age at operation. The mean follow-up time was 34 months for those aged ≤75 years and 24 months for those aged >75 years. More patients in the elderly group received an ileal conduit as urinary diversion than in the younger age-group (100% and 75%, respectively; P=0.001). Elderly patients also had lower preoperative serum albumin levels and higher CCIs. There were no statistically significant differences between the two age-groups in terms of the follow-up duration, preoperative characteristics, tumour stage, surgical approach, and length of hospital stay (Table 1).

The 30-day mortality rates were 1% in patients ≤75 years and 10% in patients >75 years; the ensuing difference was statistically different (log-rank P=0.041). There was no significant difference in the 5-year cancer-specific mortality estimates between the younger and elderly groups (33 vs 33%, P=0.956; Fig 1a). However, there were significant differences in the respective 5-year other-cause (Fig 1b) and overall (Fig 2) mortality rates, being 13% and 46% for the younger group and 47% and 80% in the older group.

TABLE 2. Cox regression analysis of overall mortality

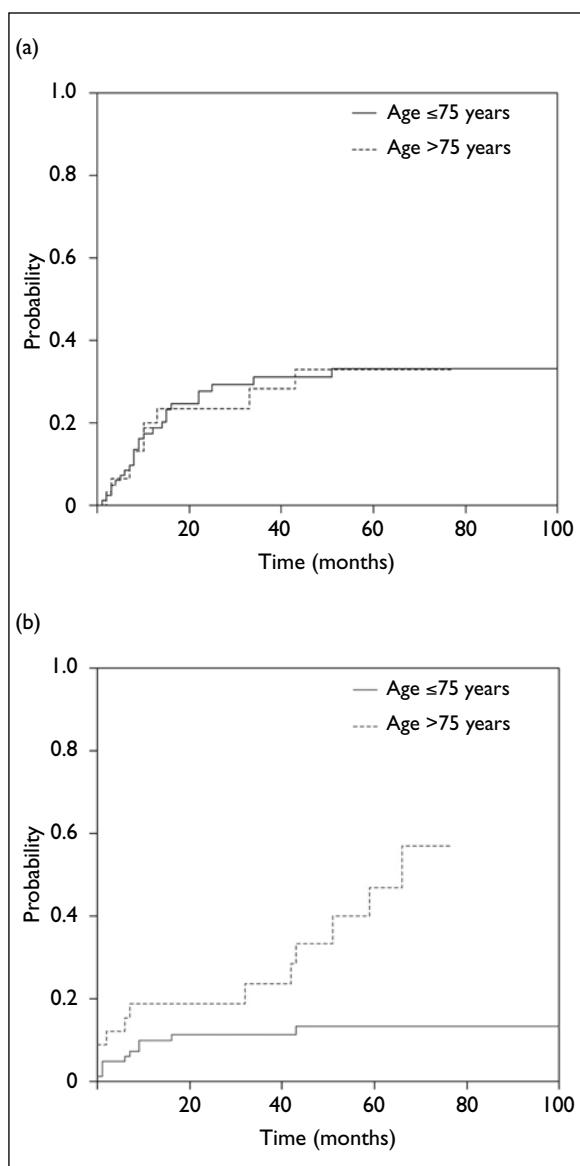|	Hazard ratio (95% confidence interval)	P value
Age (>75 years)	1.030 (1.001-1.061)	0.044
Preoperative serum albumin level (>39 g/L)	0.946 (0.902-0.992)	0.022
Tumour stage		
I	0.299 (0.130-0.687)	0.004
II	0.276 (0.116-0.653)	0.003
III	0.738 (0.384-1.417)	0.361
IV	1	-

FIG 1. The cumulative incidence curves for (a) cancer-specific mortality by age-group; the difference in incidence between the two age-groups was not statistically significant (P=0.956), and (b) other-cause mortality by age-group; the difference in incidence between the two age-groups was statistically significant (log-rank P=0.002)
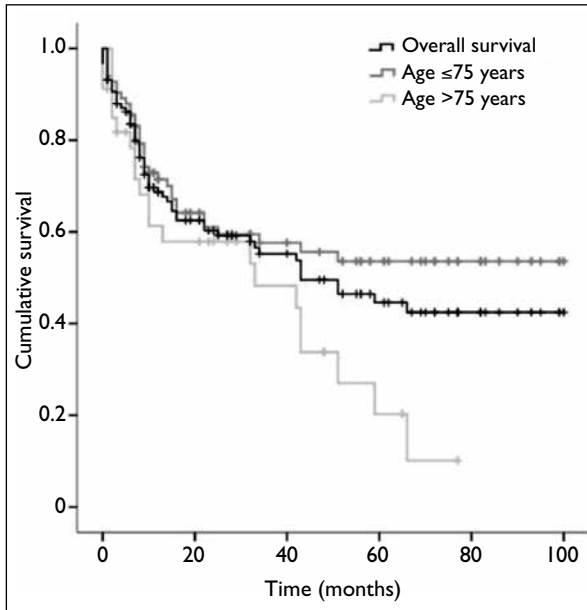
FIG 2. The Kaplan-Meier estimates for overall survival stratified by age

Patients aged >75 years had a lower 5-year overall survival than patients aged ≤75 years (P=0.023)

Cancer-specific, other-cause, and overall mortalities according to serum albumin level

The preoperative serum albumin level was a strong predictor of postoperative mortality (Fig 3). The 5-year cancer-specific, other-cause, and overall mortality rates were significantly higher in patients with preoperative serum albumin levels of ≤39 g/L, being 42%, 33% and 75%, respectively, whilst in those with higher levels the respective mortality rates were 24%, 12% and 36%.

Discussion

Bladder cancer is a disease of the elderly.[1] Almost a quarter of patients had MIBC at the time of presentation. The standard treatment for MIBC is radical cystectomy with bilateral pelvic lymph node dissection. The benefit of major surgery in advanced age remains questionable and surgeons tend to avoid cystectomy in elderly patients.[11] Reports have shown that cystectomy can be performed safely in selected elderly patients without significantly increasing complication rates or mortality.[12-14] Some series reported no significant difference between the cancer-specific and overall survival rates following cystectomy for patients younger and older than 70 years.[15] Hong Kong has one of the highest life expectancies in the world. According to the United Nations World Population Prospects, life expectancy at birth is 80 years for males and 86 years for females in Hong Kong.[7] Treatment of MIBC in elderly patients remains a challenge, especially in an ageing
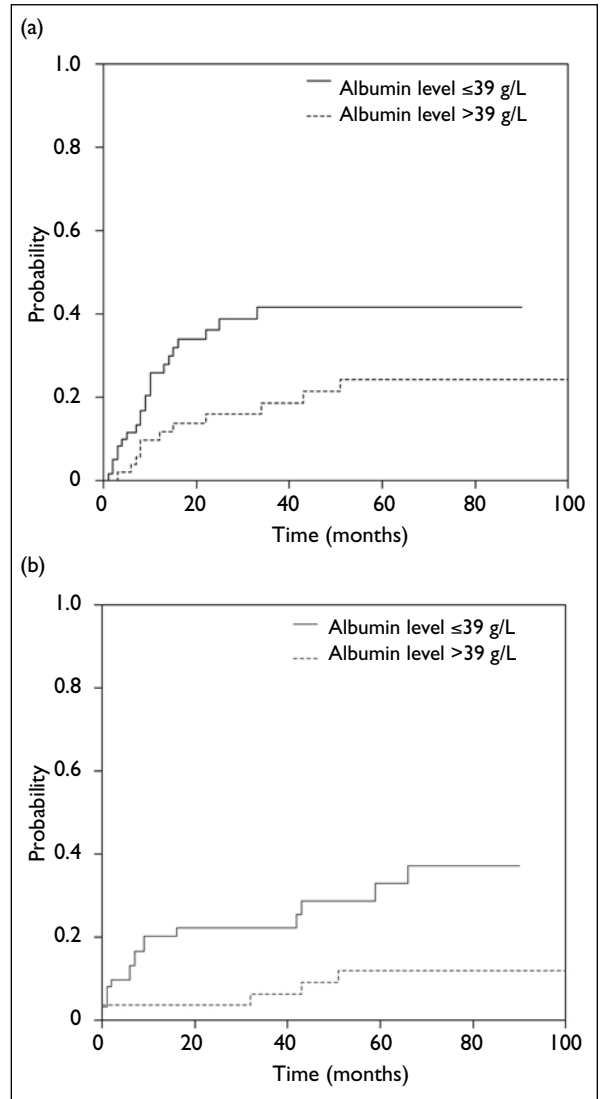

FIG 3. The cumulative incidence curves for (a) cancer-specific mortality by preoperative serum albumin level; the difference in incidence between the two age-groups was statistically significant (P=0.026), and (b) other-cause mortality by preoperative serum albumin level; the difference in incidence between the two age-groups was statistically significant (log-rank P=0.005)

population. In this study, we evaluated the predictors of survival in patients undergoing radical cystectomy.

Several studies have reported that after radical cystectomy, the median length of hospital stay for patients >75 years is longer than that for younger patients.[16,17] According to an analysis based on the Surveillance, Epidemiology and End Results registry database, when compared with younger patients, 90-day mortality after radical cystectomy was 2.8-fold higher in those aged >70 years and 5-fold higher in octogenarians.[6] In the elderly moreover, long-term outcome and survival rates are also compromised. Lughezzani et al[18] reported that both the disease stage and patient age were the predictors of survival. Age is also one of the main factors influencing other-

cause mortality,[19] which implies that after stratifying according to stage, elderly patients are more likely to die from causes unrelated to their radical cystectomy, even if their bladder cancer is cured. Our present findings are in line with such reports in the literature. Although the cancer-specific mortality rates were similar in both patient groups, other-cause mortality played the most important role in the higher overall mortality in elderly patients. This finding has important implications for the premise that radical cystectomy is the treatment of choice for MIBC in elderly patients. Thus, some surgeons may prefer TUR with radiotherapy to treat this condition in elderly patients. Chamie et al[19] reported a marginal survival benefit of 3 months for cystectomy over bladder-sparing strategies in patients aged ≥80 years. However, Faba et al[20] reported that patients with MIBC treated with TUR had a lower perioperative complication rate but higher cancer-specific mortality.

Poor nutrition is known to have a detrimental effect on postoperative outcomes.[21,22] A recent study confirmed that nutritional deficiency (preoperative serum albumin level <35 g/L, body mass index <18.5 kg/m^2, weight loss ≥5%) is a strong predictor of 90-day mortality and poor overall survival.[23] We found that a preoperative serum albumin level of ≤39 g/L was associated with worse cancer-specific, other-cause, and overall survival rates.

Limitations of our study included potential selection bias and small sample size. Cystectomy candidates with multiple co-morbidities (such as the elderly) are more likely to be offered alternatives other than major surgery. Increased co-morbidity is reported to confer increased overall mortality and cancer-specific mortality after radical cystectomy.[24] The American Society of Anesthesiologists score or Eastern Cooperative Oncology Group performance status score are commonly used as subjective measures of a patient's pre-morbid status. In our study, we used the CCI as it is a simple and valid method of estimating the risk of death. Morgan et al[25] developed a nomogram based on different preoperative clinical factors to predict survival after radical cystectomy in elderly patients. Age, CCI, tumour stage, and the preoperative serum albumin level were used to calculate the probability of 90-day survival. In the current study, CCI was not a predictor of survival according to the Cox regression model. In our cohort, however, only 2% of the patients had a CCI of ≥3 in our cohort. This is much lower than the data published by Morgan et al,[25] in which 17% of patients had a CCI of >3. Our mean follow-up duration was 31 ± 29 months. A longer follow-up is necessary to address long-term survival. Due to poor documentation in the clinical record, the status and duration of cigarette smoking were not included in our multivariate analysis. In the literature, the correlation between smoking status and outcome after radical cystectomy is controversial.[26,27] Better documentation of smoking habits is needed to assist future investigators to evaluate this issue.

Conclusion

Age at cystectomy, cancer staging, and preoperative serum albumin level are the predictors of survival after radical cystectomy. Greater other-cause mortality in elderly cystectomy patients was observed in our high longevity population. This information should be provided and discussed with patients and their relatives, before considering radical cystectomy for the treatment of MIBC.

Declaration

No conflicts of interest were declared by authors.

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