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Contemporary radical cystectomy outcomes in patients with invasive bladder cancer: a population-based study

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Objective

To determine the contemporary survival outcomes from a whole population and identify significant predictors of survival, as contemporary population-based survival outcomes after radical cystectomy (RC) for the treatment of bladder cancer (BC) are sparse. Reports suggest a large disparity between population outcomes and those of centres of excellence.

Patients and Methods

All invasive BC cases diagnosed between 2001 and 2007 in New South Wales, Australia, were identified from the Central Cancer Registry. Records of treatment and death were electronically linked. All patients who underwent RC between 2001 and 2009 were selected for this study (804 patients). Follow-up was to the end of 2009. Outcomes assessed were disease-specific survival (DSS) and overall survival (OS). Multivariable Cox regression and log-rank analysis were used to model and compare survival within groups.

Results

Of 804 patients diagnosed during the study period 420 (52.2%) died during follow-up. The 5-year DSS and OS for all patients was 59.6% and 53.2%, respectively. The 5-year DSS for patients with localised, regional and distant disease, undergoing RC was 72%, 51% and 10%, respectively. Age ($P < 0.001$) and stage ($P < 0.001$) were associated with 5-year DSS and OS after adjusting for all other variables. High-volume centres had significantly better 5-year DSS compared with low-volume centres ($P < 0.05$). The 30-day mortality for high- vs low-volume centres was 1.8% and 3.6%, respectively. Perioperative mortality improved over time for high- and moderate-volume centres but not for low-volume centres.

Conclusion

Contemporary survival outcomes after RC are much improved compared with older studies and appear close to results from academic centres of excellence. High-volume centres report better 5-year DSS outcomes than lower volume centres.

Keywords

bladder cancer, cystectomy, population, survival, volume

Introduction

Currently, radical cystectomy (RC) with bilateral pelvic lymphadenectomy is the primary treatment for patients with muscle-invasive bladder cancer (BC) or refractory, high-grade Ta, T1, Tis BC. To date several contemporary, single centre series of patients treated with RC for BC combined with bilateral lymphadenectomy have been published [1–5]. However, very few report disease-specific survival (DSS) as an endpoint. Multi-institutional series from leading academic institutions have also been published [6–8]. Combined, the results from these series raise concerns about the ability to generalise their findings to the general population, as the study populations may have differences in diagnosis, patient selection due to differential referrals, staging, pathological evaluation, type of treatment, and quality of treatment.

The results from population-based studies are probably more reflective of expected clinical outcomes in the general population, which includes academic, as well as community treatment centres.

We report on an Australian population of invasive BC diagnosed between 2001 and 2007, and treated with RC between 2001 and 2009. The aim of the present study was to describe DSS and overall survival (OS), and factors associated with each, after RC in a population-wide setting.

Patients and Methods

Data for all cases of BC diagnosed in New South Wales (NSW) residents were obtained from the NSW Central Cancer Registry (CCR). Operational details of the Registry have been described previously [9]. Notifications to the CCR of invasive BC (ICD-10 code: C67) diagnosed in NSW are mandated from pathology laboratories, hospitals and other treatment centres under the NSW Public Health Act 1991 [9]. For this study all registered cases diagnosed between January 2001 and December 2007 were eligible. Hospital admission and treatment details were retrieved by linkage to the NSW Admitted Patient Data Collection (APDC) on all hospital separations in NSW in the period January 2001 to end of June 2009. This was the most recent data available at time of analysis and the period for RC was increased to 2009 to allow for patients having delayed RC for reasons such as BCG treatment. Hospital medical coders abstracted individual patient information from medical records after the patient's discharge from any hospital in the state of NSW. This includes dates of admission and separation, procedures undertaken, and diagnoses relating to the hospital episode. Only patients with BC who had a record of a RC were included in this study. Death information was obtained by electronic linkage of the records from the CCR with NSW death records from the Registry of Births Deaths and Marriages (January 2001 to mid-December 2009) and Australia Bureau of Statistics (January 2001 to mid-December 2007). The cause of death was determined from the death certificate. Linkage of records in these data sets was carried out by the Centre for Health Record Linkage (CHeReL), using probabilistic matching using ChoiceMaker software (ChoiceMaker Technologies Inc., New York, USA). This linkage was performed using name, address, date of birth, date of diagnosis, and hospital-recorded clinical information that identified cases common to all data sets, and clerical reviews for questionable matches were undertaken by trained staff within the CHeReL.

Patients diagnosed with BC were classified by: (i) age at diagnosis, categorised in decades; (ii) socio-economic status, five ordinal categories using the residential local government area-based Socio-economic Index of Relative Disadvantage for Areas [10]; (iii) five ordinal categories using the residential local government area-based Accessibility/Remoteness Index of Australia (ARIA) [11]; (iv) country of birth, Australian New Zealand born, Europe, Asia and Other. Two patients (0.25%) with unknown country of birth were grouped with 'Other'; (v) Year of diagnosis was grouped into five periods for statistical analysis; (vi) degree of spread at diagnosis was based on the CCR classification of stage at first presentation. This was determined as the maximum extent of the BC based on all reports and notifications received by the CCR within 4 months of diagnosis. This classification follows the international coding guidelines for summary stage adopted by the WHO and the International Association of Cancer Registries [12]. Extent was grouped as localised (cancer was limited to bladder – Stage I and II), regional (cancer extended outside the bladder locally – Stage III and some IV), distant (cancer in regional lymph nodes or distant metastases – Stage IV), or unknown degree of spread. The Charlson comorbidity index (CCI) was used to categorise comorbidity. Hospital volume (RCs/year) was categorised into low- (≤3), moderate- (4–6) and high-volume (>6) based on the analysis by Birkmeyer et al. [13,14].

The percentages of patients dying from BC within 5 years of diagnosis were calculated using Kaplan–Meier product-limit estimates. Multivariable survival analyses were performed with the Cox proportional hazard regression model. Trends in perioperative mortality were analysed by multiple regression. Statistical significance in this study was considered at $P < 0.05$. All reported P values are two-sided. Patients who were alive at the end of the study were censored at mid-December 2009. All analyses were carried out in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

NSW Population and Health Services Research Ethics Committee approved this study (#2010/04/223).

Results

The demographic, clinicopathological and surgery characteristics of 804 patients who underwent RC for BC within the study period are detailed in Table 1. The median follow-up for patients who remained alive was 62.5 months. Patients with localised BC comprised the largest group (353, 43.9%) followed by those with regional disease (324, 40.3%). The extent of disease was unknown in 10.7% of patients (coder had insufficient imaging and pathological information). In all, 420 of 804 (52.2%) patients diagnosed in the study period died during the period of follow-up. Of these deaths, 289 (36%) were due to BC and 131 (16.3%) from other causes. Most patients had their surgery in a low- or moderate-volume (<7 RCs/year) hospital. There were 39 hospitals in the State that performed between 1 and 3 RCs/year. There was an association between patients resident in metropolitan areas having surgery in moderate- or high-volume centres and rural patients having surgery in low-volume centres ($P < 0.001$). At the time of operation, 291 patients (36.2%) did not receive a lymph node dissection (LND) and there was a strong association between higher volume centres and the performance of LND ($P < 0.001$).

Factors Associated with a Decrease in Survival after RC

The estimated 5-year DSS and OS for the whole patient cohort was 59.6% and 53.2%, respectively. The 5-year DSS for patients with localised, regional and distant disease, undergoing RC was 72%, 51% and 10%, respectively. The 5-year DSS was

Table 1 Patient characteristics for all NSW residents diagnosed with BC in 2001–2007 and who had a RC in 2001 to 2009 with follow-up to 2009.

Variable	*N* (%)
Number of patients	804 (100)
Age, years	
<50	42 (5.2)
50–59	108 (13.4)
60–69	245 (30.5)
70–79	339 (42.2)
≥80	70 (8.7)
Gender	
Females	194 (24.1)
Males	610 (75.9)
Socio-economic status	
Least disadvantaged (Q1)	191 (23.8)
2nd least disadvantaged (Q2)	129 (16.0)
Middle (Q3)	178 (22.1)
2nd most disadvantaged (Q4)	145 (18.0)
Most disadvantaged (Q5)	161 (20.0)
Geographic location	
major cities	596 (74.1)
inner regional	159 (19.8)
outer regional/Remote	49 (6.1)
Country of birth	
Australia/New Zealand	513 (63.8)
Europe	219 (27.2)
Asia	20 (2.5)
Other	52 (6.5)
CCI	
0	520 (64.7)
1	123 (15.3)
≥2	161 (20.0)
Extent of disease	
Localised	353 (43.9)
Regional	324 (40.3)
Distant	41 (5.1)
Unknown	86 (10.7)
Death	
Total	420 (52.3)
From BC	289 (36.0)
From other causes	131(16.3)
Time to RC, days	
0–90	493 (61.3)
>90	311 (38.7)
Centre volume	
Low (1–3 RCs/year)	374 (46.5)
Moderate (4–6 RCs/year)	375 (46.6)
High (≥7 RCs/year)	55 (6.8)
Hospital type	
Public	489 (60.8)
Private	315 (39.2)
Lymph node dissection (LND)	
Yes	513 (63.8)
No	291 (36.2)

associated with age ($P < 0.001$; Fig. 1), stage ($P < 0.001$; Fig. 2), CCI ($P = 0.008$; Fig. 3), gender ($P = 0.009$), and status of LND ($P = 0.02$) by log-rank test. The 5-year OS was associated with age ($P < 0.001$; Fig. 1), stage ($P < 0.001$; Fig. 2), gender ($P = 0.09$), CCI ($P < 0.001$), and status of LND ($P = 0.04$).

In a multivariable cox regression analysis, age ($P < 0.001$) and stage ($P < 0.001$) were significant predictors of DSS and OS, and CCI also predicted OS ($P < 0.001$) (Table 2). The likelihood of DSS was improved by 44% (hazard ratio 0.56, 95% CI 0.32–0.95) in a high-volume hospital compared with a low-volume hospital. However, being female, having private hospital insurance, and absence of LND were not significantly associated with DSS or OS after controlling for other variables.

Perioperative Mortality

In all, 50 hospitals performed one or more RCs during the study period. These were divided into low- (0–3 RCs/year), moderate (4–6 RCs/year) and high-volume (>6 RCs/year) hospitals. The 30- and 90-day mortality was calculated and is shown in Fig. 4. Perioperative mortality in low-volume hospitals visually appeared to be higher than high-volume hospitals; however, this was not statistically significant at 30 ($P = 0.113$) or 90 days ($P = 0.982$). In addition, both 30- ($P = 0.006$) and 90-day ($P = 0.005$) mortality showed a trend of improving rates over the years. In the high-volume centres perioperative mortality was low at 1.8% for 30-day and 3.6% for 90-day mortality vs 4.3% and 6.4% for the low-volume centres.

Discussion

We report for the first time, contemporary population-based outcomes for RC in the state of NSW, Australia between 2001 and 2009. The 5-year DSS and OS of 60% and 53% respectively are among the highest whole population survival outcomes reported; however, the absence of LND and poorer DSS in patients undergoing RC in low-volume compared with high-volume centres, raise the prospect of improving these outcomes further.

Very few population-based studies reporting outcomes of RC have been published to date. Whole population reports are important to determine representative and current outcomes in a population, which allow us to identify problems and implement changes. They avoid the biases that single and multi-institutional studies from centres of excellence experience, such as referral bias and case selection, disease spectrum treated, diagnostic and management differences, which are unlikely to accurately represent the patterns of care and outcomes in the general community and especially low-volume centres.

Compared with other contemporary reported outcomes from whole populations, patients undergoing RC in NSW fared well. A study from the Ontario Cancer Registry reported 5-year DSS after RC to be 33% [15]. Another study from the Eindhoven Cancer Registry, reported the 5-year relative survival after RC to be 48% [16] and a study from northern Netherlands also reported a 5-year DSS after RC of 54% [17]. The Surveillance, Epidemiology and End Results (SEER) programme from the USA have reported 5-year DSS to be 64% after RC [18].

Compared with older historical population outcomes, the NSW survival outcomes are substantially better. A study from

Fig. 1 Kaplan–Meier survival curves stratified by age group at diagnosis.

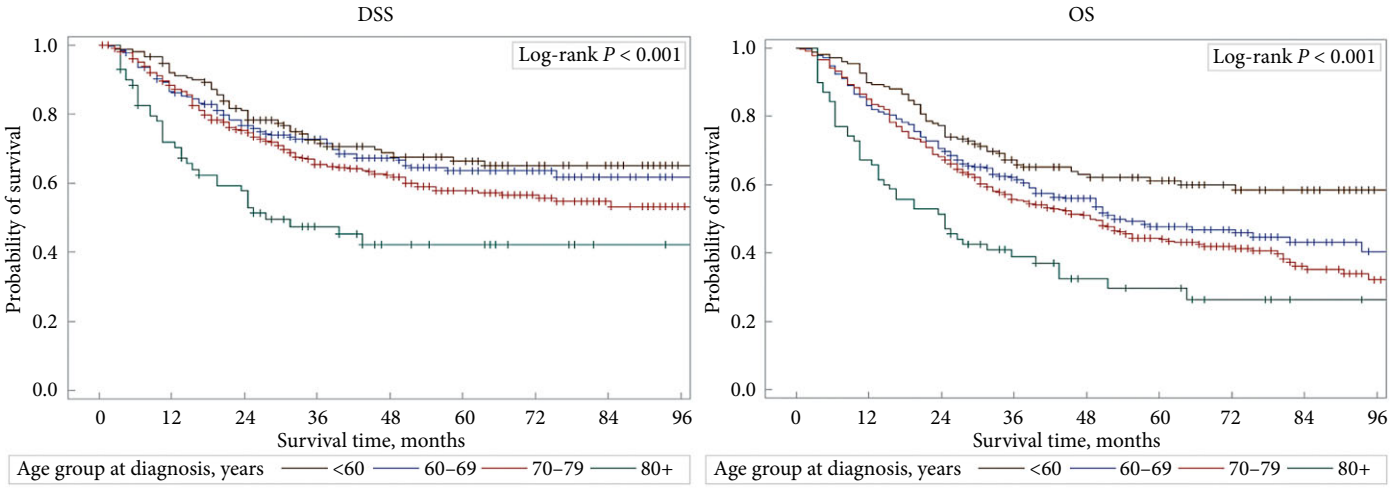
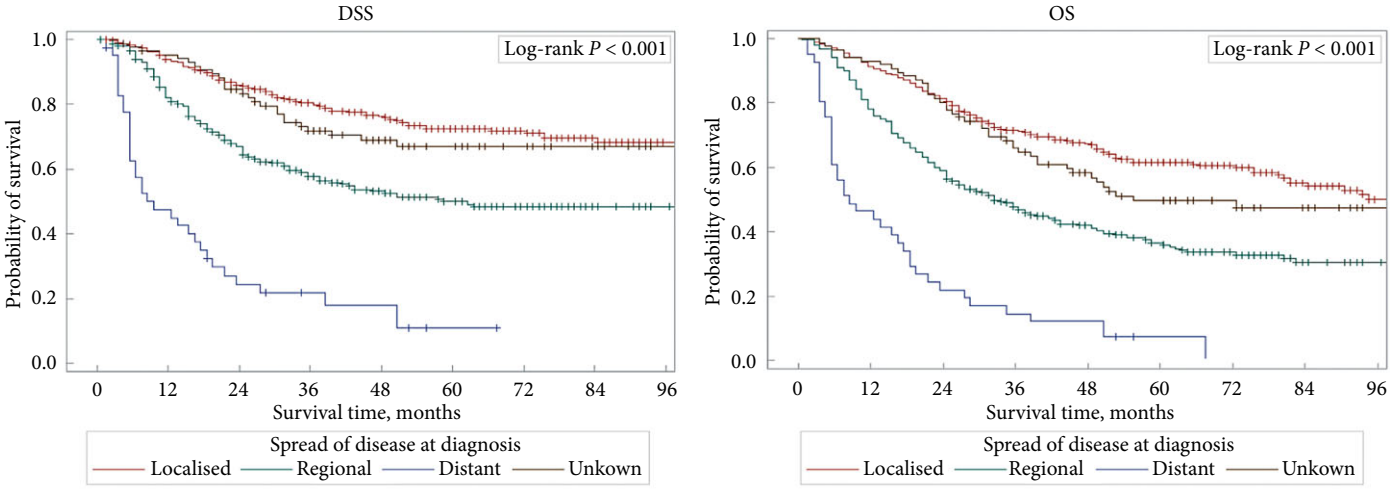


Fig. 2 Kaplan–Meier survival curves stratified by stage of disease at diagnosis.



the Yorkshire Cancer Registry from 1993 to 1996 reported an OS of only ≈30% compared with our present study where OS at 5 years was 53% [19]. A population study from 1990 to 1995 in Victoria, Australia reported 5-year DSS and OS after RC of only 28% and 13% [20]. As the populations, hospital systems, and urologist training between these two Australian States were similar; it is plausible that there has been a substantial improvement in RC outcomes over time in Australia. Interestingly, there has not been an improvement in outcomes from academic institutions over three decades, which is probably due to high levels of surgical care delivered in these institutions, leaving little room for improvement [21].

Major academic institutions have generally reported outcomes results based on pathological stage, which has made clinical staging comparisons in population series difficult. The Bladder Cancer Research Consortium, which included 21 international academic institutions, reported 5-year DSS after RC in 2012 of ≈60% for all pathological stages [22], which is the same as our present population series. The same group has recently reported the 5-year DSS on 8141 RC patients from 15 academic institutions to be 68% [23]. In our present study, 5% of patients having RC had distant disease and we presume the surgery was for palliative reasons. The 5-year DSS and OS of 10% in these patients compares favourably with 5.5% survival data from the SEER registry [24] and also to 13.5% from patients undergoing methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) chemotherapy in a trial for advanced BC [25].

In our present study, well-defined factors such as age, stage, and comorbidity were associated with survival. We were unable to evaluate the impact of neoadjuvant or adjuvant chemotherapy, as the dataset may have been incomplete.

Fig. 3 Kaplan–Meier survival curves stratified by CCI score at diagnosis.

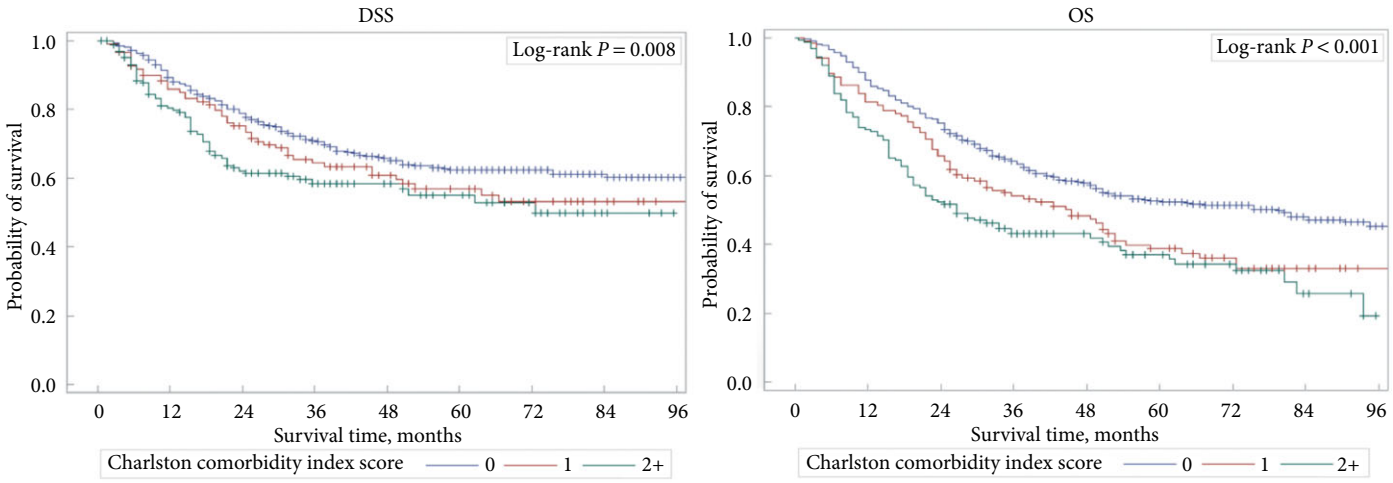


Table 2 Multivariable analysis of factors associated with DSS and OS after RC for BC.

Factor	DSS HR (95% CI)	*P*	OS HR (95% CI)	*P*
Age, years				
<60	1	<0.001	1	<0.001
60–69	1.24 (0.86–1.80)		1.64 (1.20–2.26)	
70–79	1.36 (0.96–1.90)		1.70 (1.26–2.29)	
≥80	2.54 (1.62–3.96)		2.78 (1.87–4.13)	
Stage				
Localised	1	<0.001	1	<0.001
Regional	2.26 (1.72–2.96)		2.07 (1.66–2.59)	
Distant	8.92 (5.89–13.5)		6.73 (4.64–9.77)	
Unknown	1.20 (0.78–1.87)		1.23 (0.87–1.74)	
Female sex	1.22 (0.94–1.58)	0.134	1.11 (0.88–1.38)	0.381
CCI				
0	1	0.059	1	<0.001
1	1.35 (0.98–1.87)		1.46 (1.12–1.90)	
≥2	1.34 (1.00–1.80)		1.56 (1.23–1.99)	
Centre volume				
Low (0–3 RCs/year)	1	0.058	1	0.483
Moderate (4–6 RCs/year)	0.83 (0.65–1.07)		0.91 (0.74–1.12)	
High (≥7 RCs/year)	0.56 (0.32–0.95)		0.82 (0.56–1.21)	
Private hospital	1.01 (0.78–1.3)	0.968	0.90 (0.72–1.11)	0.326
LND (absent)	1.23 (0.97–1.57)	0.092	1.18 (0.96–1.44)	0.112

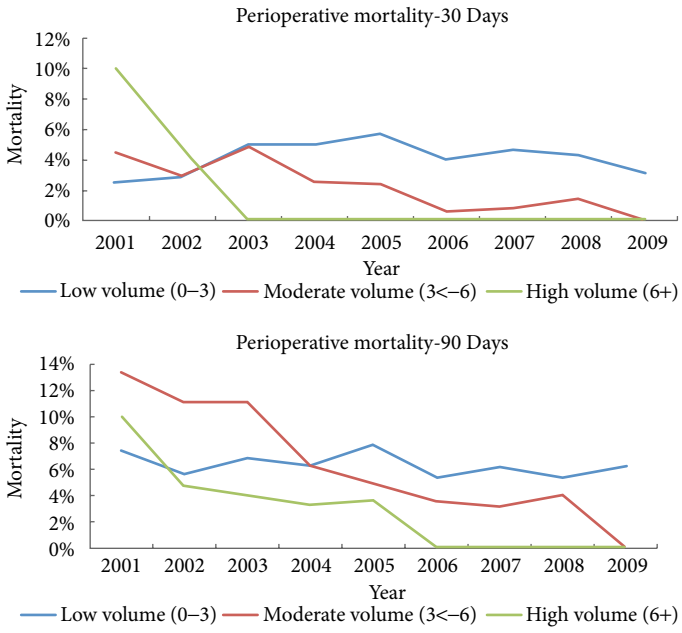
HR, hazard ratio.

Although female gender has been shown to be associated with worse BC survival in NSW [26], this has been questioned in a RC cohort [27] and was also not a significant factor in the present study. We have previously shown that gender differences only exist in those aged >70 years and RC cohorts tend to be younger (in press Cancer Medicine).

We did not evaluate the variable of time to RC, as our cohort included a small number of patients with pT1 disease that cannot be separated from those with muscle invasion, but would skew the expected effect of time to RC.

Although outcomes from RC in NSW appear better or comparable to contemporary populations studies and close to leading academic institutions, the quality of surgery can be questioned, as there was no record of LND having been performed in 36% of cases and we were unable to obtain the pathological details of those that did have a LND. A separate in-depth pathological analysis by our group on a subset of 201 of these patients did however confirm that ≈30% did not receive a LND and only 17% had >10 nodes retrieved at LND [28]. There was a significant difference in DSS and OS in those that had a LND on univariate analysis, but not on multivariable analysis. The importance of an extended LND with RC has been reported in several retrospective studies, which suggest that it can improve survival [29,30] and currently two randomised trials are underway aiming to

Fig. 4 Rolling 3 year average of the percentage of patients experiencing 30- and 90-day mortality after RC by hospital volume.



confirm this benefit [31]. It is possible that with the implementation of mandatory LND standards or centralisation of RC to high-volume centres the survival outcomes could be improved even further.

Further improvements in the outcomes of patients undergoing RC for BC in NSW may be gained from presentation of their case in multidisciplinary meetings, as this has been shown to change management plans in ≈25% of cases [32]. We do not have reliable data on the proportion of patients who received perioperative chemotherapy but suspect it is low, as has been reported by Liew et al. [33].

Perioperative mortality after RC has been reported to be 0.3% to 7.9% [34–37]. Hospital volume and surgeon volume have been shown to be significant factors determining mortality after this major operation [38]. In a systematic review and meta-analysis of seven reported studies, high-volume hospitals had a 45% lower rate of perioperative mortality compared with low-volume hospitals. The definition of low-volume ranged from 1 to 9 RCs/year and high-volume 4–24 RCs/year. Our present study found differences that were not statistically significant for 30- and 90-day perioperative mortality between high-and low-volume hospitals. However, there was a decrease in perioperative mortality rates in moderate- and high-volume centres over time ($P < 0.05$) and they have been 0% in high-volume centres since 2006. More importantly, we found that 5-year DSS was 44% higher in patients who had RC in a high-volume compared with low-volume centre, which has obvious healthcare delivery implications. It was concerning that of 50 hospitals performing RC, 39 are performing <4 RCs/year; with most of these hospitals performing one or less per year. Our observation that there was an association between place of residence and surgery in a high-volume hospital suggests that centralisation of RC services has not occurred in NSW. The effect that this has on cancer outcomes is not known currently and the subject of ongoing research by our group, but rural residence has been shown to be associated with poorer outcomes in patients with prostate cancer in Australia [39,40]. Future policies should be directed towards evaluating individual hospital outcomes and restricting the performance of RC to high-volume hospitals if necessary. Individual surgeon data are not available to determine if surgical experience or surgeon volume also had an impact on perioperative mortality; however, this may not be an independent predictor of perioperative mortality or survival when hospital volume is adjusted for [41].

The present study's strength is that it is population based and collected every diagnosed BC in the State during the study period. The results are generalizable to the whole State, and possibly the country, not just academic centres, where most outcomes studies originate. In addition, every inpatient admission is recorded through high-quality data linkage resulting in reliable levels of surgical treatment ascertainment. However, the present study does have several limitations that may bias the results. The first, potential inaccuracies in the staging of patients in the present study, as the accuracy of staging information collected cannot be confirmed. Secondly, the cancer registry codes cT1 and cT2, organ-confined BC together as localised, thus cT2 BCs cannot be separately analysed or compared with other studies. Thirdly, we were unable to obtain detailed RC pathological information, which would have been useful to allow in-depth analysis of quality of surgery.

In conclusion, the present contemporary population based study of RC has shown DSS and OS rates superior to other older and contemporary population-based series and close to outcomes from centres of excellence. In addition to age and stage, high hospital volume reduces the 5-year DSS by 44% compared with low-volume centres. Improvements in outcomes could possibly be gained from improving quality of RC and limiting surgery to high-volume hospitals.

Conflicts of Interest

None disclosed.

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Abbreviations: BC, bladder cancer; CCI, Charlson comorbidity index; CCR, Central Cancer Registry; CHeReL, Centre for Health Record Linkage; DSS, disease-specific survival; LND, lymph node dissection; NSW, New South Wales; OS, overall survival; RC, radical cystectomy; SEER, Surveillance, Epidemiology and End Results.