ORIGINAL ARTICLE

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Outcomes following radical cystectomy: a population-based study from Queensland, Australia

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Key words
bladder cancer, mortality, population-based, radical cystectomy.

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Accepted for publication 2 April 2019.

doi: 10.1111/ans.15259

Abstract

Background: Radical cystectomy (RC) is a complex uro-oncology surgical procedure with high surgical morbidity. We report on outcomes following RC for bladder cancer using a population-based cohort of patients.

Methods: Patients receiving an RC from 2002 to 2016 were included and linked to their cancer-related surgical procedures. Hospitals were categorized as high (>7 RCs/year) and low (≤7 RCs/year). Outcomes included 30- and 90-day mortalities and 2-year overall survival (OS). Multivariable logistic regression models were used to examine factors associated with the outcomes of interest. OS was estimated using the Kaplan–Meier survival function.

Results: During the 15-year study period, 1230 patients underwent an RC for invasive bladder cancer. In-hospital mortality was 1.1%, and 30- and 90-day mortality was 1.4% and 2.9%, respectively. Both 30- and 90-day mortalities were significantly higher for older versus younger patients ($P = 0.01$ and $P < 0.001$, respectively), and lymph node involvement was significantly associated with 90-day mortality ($P = 0.002$). Patients treated more recently were about 80% less likely to die within 90 days. The 2-year OS was 71.5%, with significant improvements observed over time ($P < 0.001$). While we found no evidence of a hospital-volume relationship for post-operative mortality or survival, patients treated in low-volume compared to high-volume hospitals were more likely to have surgical margin involvement (10.9% versus 7.1%, respectively, $P = 0.03$).

Conclusion: We observed low post-operative mortality rates overall, with rates decreasing significantly over time. Some subgroups of patients experience poorer post-operative outcomes. Reporting on post-operative outcomes, and survival over time helps monitor clinical progress and identify areas for improvement.

Introduction

In Australia in 2014, 2748 individuals were diagnosed with invasive bladder cancer (age-standardized rate = 10.1/100 000).[1] The primary treatment for patients with muscle invasive bladder cancer or those with refractory, high-grade Ta, T1 or Tis is radical cystectomy (RC).[2] RC is one of the most complex uro-oncology surgical procedures with surgical morbidity of around 50% and perioperative mortality up to 8%.[3,4]

It has been well established that complex surgical procedures when conducted in high-volume hospitals results in improved patient outcomes.[5] Evidence is also growing of an inverse relationship between outcomes and hospital and surgeon volume following RC.[3,4,6]

Few studies examining outcomes following RC have been conducted in Australia,[7–9] and none to date have been conducted in Queensland, Australia's most decentralized state where around 40% of the population live outside the state capital.[10] The development of our Cancer Quality Index through Cancer Alliance Queensland[11] provides a structure for reporting on outcomes following major cancer surgery in public and private hospitals throughout Queensland.

We report on 30- and 90-day post-operative mortalities and 2-year survival following RC for invasive bladder cancer using a population-based cohort of patients from 2002 to 2016.

Methods

This retrospective population-based study used linked data from the Queensland Oncology Repository. Queensland Oncology Repository consolidates patient information for Queensland and contains data on cancer diagnoses from the Queensland Cancer Register and treatment from the Queensland Hospital Admitted Patient Data Collection for Queensland public and private hospitals. Death data were obtained from births, deaths and marriages with cause of death coded by the Australian Bureau of Statistics.

Study population

The study included individuals diagnosed with a new case of bladder cancer (International Classification of Diseases for Oncology (3rd edition) site code (C67)) between 2002 and 2016 who underwent an RC (total excision) from 2002 to 2016. Cancer-related surgical procedures were identified and reviewed by expert clinicians and categorized. All data used in this analysis were de-identified.

Variables included

We included age, sex, cancer type, stage at diagnosis and type of hospital (public or private). Socio-economic status was assigned according to the Australian Bureau of Statistics Socio-Economic Indexes for Areas.[12] Residence at the time of diagnosis was categorized into metropolitan or rural, based on the Australian Geographical Classification.[13] We conducted a review of all available pathology reports and used the Union for International Cancer Control 7th edition classification to assign stage at diagnosis. Stage was categorized as Tis-II and III–IV (stage was unavailable for 19 (1.5%) cases). Information on margin status, number and positivity of lymph nodes excised at the time of RC was also extracted. Charlson co-morbidity score[14] was derived from hospital admission data and included any co-morbid condition in the period 1 month prior to, and up to 12 months after surgery. Hospital volume was categorized as high (>7 RCs/annually) and low (≤7 RCs/annually), based on those used in a previous Australian state-based study.[8] Year of surgery was categorized into three periods: 2002–2006, 2007–2011 and 2012–2016.

Outcome variables

Thirty-day and 90-day post-operative mortalities from the date of procedure included all causes of death. Two-year and 5-year overall survival (OS) rates were calculated from the date of surgery with follow-up to 31 December 2018.

Analysis

The statistical significance of bivariate comparisons between 30- and 90-day mortalities, and various sociodemographic and clinical factors was estimated using the chi-squared or Kruskal–Wallis test. Multivariable logistic regression models were constructed to examine factors independently associated with the outcomes of interest. For each model we included sex, age, co-morbidities, American Society of Anesthesiologists physical status classification system, hospital volume, type of hospital (public or private), stage at diagnosis, lymph node status, surgical margins and period of surgery. Models were adjusted for within-hospital clustering. Observed 2- and 5-year post-surgical OS was estimated using the Kaplan–Meier survival function. Multivariable analyses were performed with Cox proportional hazards regression model to examine factors associated with risk of death within 2 years of surgery. All analyses were conducted using Stata V15.1 (StataCorp, College Station, TX, USA).

Results

From 2002 to 2016, a total of 1230 individuals received an RC. Of the cohort, 77.0% were male and median age was 67 years (range 29–89). Table 1 provides information on the sociodemographic and clinical factors of the cohort. Up to the end of the follow-up period (31 December 2018), 53.6% of the cohort had died.

Outcomes following radical cystectomy

Thirteen (1.1%) in-hospital deaths occurred, 14 (1.1%) and 36 (2.9%) patients died within 30 and 90 days of RC, respectively. Figure 1 shows the number of deaths plotted against the number of RCs performed over three time periods. From 2002 to 2006, 30-day mortality was 2.6%, decreasing to 0.8% during 2012–2016 ($P = 0.008$). Ninety-day mortality for 2002–2006 was 5.4% decreasing to 1.4% for 2012–2016 ($P = 0.004$).

Lymph node and surgical margin status

Overall, 70.8% of patients ($n = 871$) had a lymph node dissection and the median number of nodes removed was 7 (range 1–73). Positivity rate was 22.8% and this was similar across hospital volumes. In multivariate analysis, compared to patients from affluent areas, those from middle and disadvantaged areas were less likely to have had lymph node dissection (OR 0.46, 95% CI 0.28–0.75 and OR 0.44, 95% CI 0.23–0.84, respectively). Lymph node dissection was more likely for public, compared to private hospital patients (OR 2.69, 95% CI 2.10–3.44) and for patients whose RC was performed during 2012–2016 compared to 2002–2006 (OR 2.95, 95% CI 1.76–4.94). There was no significant association with hospital volume (data not shown).

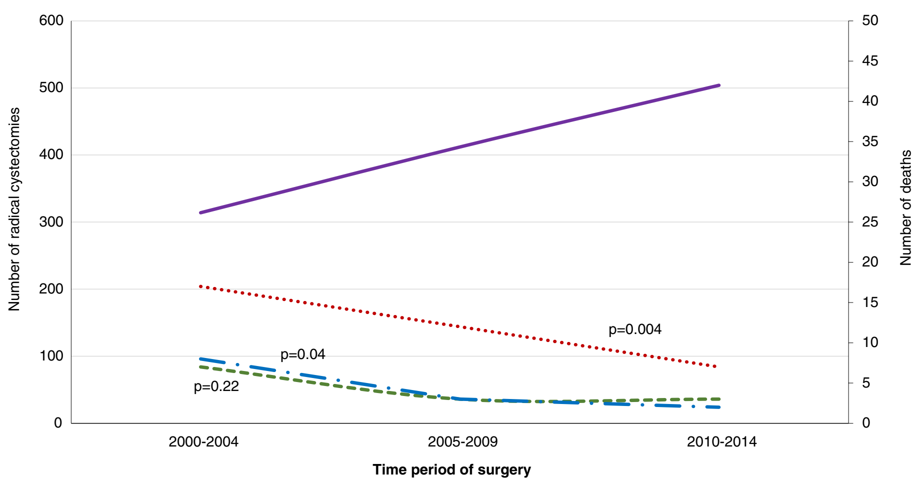
Bladder surgical margins (*in situ* or invasive) were involved in 9.7% of patients with known margin status ($n = 1220$ (99%)). Surgical margin involvement was higher for patients from low-volume compared to high-volume hospitals (10.9% versus 7.1%, respectively, $P = 0.03$). There was no difference in rates of surgical margin involvement over time.

Table 1 Factors associated with 30- and 90-day mortalities following radical cystectomy

	Patients = 1230	30-day mortality (*n* = 16)		90-day mortality (*n* = 44)	
	n (%)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex			0.20		0.53
Female	283 (23.0)	1.00		1.00	
Male	947 (77.0)	4.06 (0.47–35.38)		1.36 (0.52–3.50)	
Age group			0.01		0.003
<65 years	477 (38.8)	1.00		1.00	
65–74 years	510 (41.5)	1.16 (0.18–7.37)		1.53 (0.68–3.43)	
≥75 years	243 (19.8)	6.52 (1.64–25.87)		3.39 (1.81–6.37)	
Residential location			0.85		0.38
Metropolitan	771 (62.7)	1.00		1.00	
Rural	459 (37.3)	0.89 (0.24–3.21)		0.67 (0.27–1.63)	
Socio-economic status			1.00		0.66
Affluent	1587 (12.9)	1.00		1.00	
Middle	778 (63.3)	0.93 (0.16–5.51)		1.64 (0.30–8.93)	
Disadvantaged	294 (23.9)	0.96 (0.07–12.97)		2.49 (0.30–22.21)	
Stage†					0.007
Stage Tis-II	799 (65.0)	N/A		1.00	
Stage III–IV	412 (33.5)			3.79 (1.59–9.00)	
Lymph node status			0.31		0.002
Negative	672 (54.6)	1.00		1.00	
1+ positive	199 (16.2)	0.48 (0.09–2.70)		5.84 (2.15–15.85)	
No dissection	359 (29.2)	1.85 (0.45–7.58)		1.93 (0.79–4.72)	
Margins involved‡			0.29		0.42
No	1102 (90.3%)	1.0		1.00	
Yes	118 (9.7%)	2.41 (0.47–12.50)		2.12 (0.79–5.76)	
ASA			0.06		0.24
Normal/mild disease	555 (45.1)	1.00		1.00	
Severe disease	418 (34.0)	0.19 (0.04–0.82)		1.31 (0.69–2.49)	
Unknown	257 (20.9)	0.32 (0.07–1.49)		0.56 (0.15–2.09)	
CCI			0.21		0.64
0	646 (52.5)	1.00		1.00	
1	379 (30.8)	2.04 (0.59–7.01)		1.65 (0.55–4.97)	
≥2	205 (16.7)	1.03 (0.15–6.83)		1.62 (0.53–4.99)	
Type of hospital			0.54		0.18
Private	612 (49.8)	1.00		1.00	
Public	618 (50.2)	1.53 (0.46–5.32)		1.56 (0.82–2.97)	
Hospital volume			0.99		0.23
High (>7/year)	373 (31.8)	1.00		1.00	
Low (≤7/year)	624 (53.3)	0.99 (0.28–3.51)		1.47 (0.78–2.75)	
Year of surgery			0.04		0.008
2002–2006	314 (25.5)	1.00		1.00	
2007–2011	412 (33.5)	0.08 (0.01–0.78)		0.46 (0.17–1.24)	
2012–2016	504 (41.0)	0.33 (0.09–1.19)		0.24 (0.09–0.59)	

†Stage unknown for 19 patients. ‡Margin status unknown for 10 patients. ASA, American Society of Anesthesiologists; CCI, Charlson co-morbidity score; CI, confidence interval; N/A, not included in final model; OR, odds ratio.

Fig. 1. Radical cystectomies (——) and the number of deaths in-hospital (------), and within 30 (——) and 90 days (··········) over time.



Factors associated with 30- and 90-day surgical mortality

Individuals aged ≥75 years were at higher risk of 30-day mortality compared to those under 65 years (OR 6.52, 95% CI 1.64–25.87). Risk of 30-day mortality was lower for patients treated more recently ($P = 0.04$). However, these results were based on a small number of deaths ($n = 14$). Ninety-day mortality was significantly higher for older patients (≥75 years) compared to those <65 years (OR 3.39, 95% CI 1.81–6.37) and for patients with positive lymph nodes (OR 5.84, 95% CI 2.15–15.85). Ninety-day mortality was about 75% lower for patients treated during 2012–2016 compared to 2002–2006 (OR 0.24, 95% CI 0.09–0.59).

Overall survival

The 1-, 2- and 5-year post-surgical OS was 83.0%, 71.5%, and 56.0%, respectively. The 2-year Kaplan–Meier survival curves by age group, stage, lymph node status and year of surgery are presented in Figure S1. Significant differences were found in 2-year OS for age group, stage, lymph node status and period of surgery (unadjusted). After adjustment, age ($P = 0.003$), stage ($P < 0.001$), positive lymph nodes ($P \leq 0.001$), no lymph node dissection ($P = 0.003$), involvement of surgical margins ($P < 0.001$) and higher co-morbidity burden ($P = 0.01$) were all significantly associated with poorer OS. Patients having an RC during 2012–2016 were about 40% less likely to die within 2 years of their surgery compared to 2002–2006 ($P < 0.001$) (Table 2). No association with hospital volume was found. Similar results were observed for 5-year OS (data not shown).

Table 2 Factors associated with 2-year overall surgical survival† following radical cystectomy

Variable	Overall survival, HR (95% CI)	*P*-value
Age group		0.003
<65 years	1.00	
65–74 years	0.95 (0.73–1.22)	
≥75 years	1.49 (1.12–1.97)	
Stage		<0.001
Stage Tis-II	1.00	
Stage III–IV	2.17 (1.73–2.73)	
Lymph node status		<0.001
Negative	1.00	
1+ positive	3.79 (2.92–4.93)	
No dissection	1.47 (1.12–1.93)	
Surgical margins involved		<0.001
No	1.00	
Yes	1.83 (1.35–2.46)	
CCI		<0.001
0	1.00	
1	1.06 (0.82–1.36)	
2+	1.71 (1.28–2.28)	
Hospital type		0.03
Private	1.00	
Public	1.34 (1.03–1.73)	
Hospital volume		0.59
High (>7/year)	1.00	
Low (≤7/year)	0.92 (0.70–1.23)	
Year of surgery		0.001
2002–2006	1.00	
2007–2011	0.78 (0.60–1.02)	
2012–2016	0.53 (0.41–0.70)	

†Cox proportional hazards model adjusted for the above variables as well as sex, residential location, socio-economic status and American Society of Anesthesiologists. CCI, Charlson co-morbidity score; CI, confidence interval; HR, hazard ratio.

Discussion

In this population-based study of 1230 RC patients, in-hospital, 30- and 90-day mortalities were comparable if not better than results reported elsewhere. In-hospital mortality was 1.1%, 30-day mortality 1.4% and 90-day mortality was 2.9%. Other population-based studies have reported in-hospital mortality rates of around 2.0–3.5% and 30-day mortality between 3.0% and 5.5%.[15,16] One previous Australian state-based study reported an in-hospital mortality rate of 2.2%.[9] While overall the number of in-hospital, 30- and 90-day deaths over the 15 years of the study were relatively few, we did observe a reduction in deaths over time despite a significant increase in the number of RCs over the same period. The magnitude of this reduction was similar to a large UK study, where 30- and 90-day mortalities decreased from 5.2% to 2.1% and from 10.3% to 5.1%, respectively, from 1998 to 2010.[17]

Unlike others,[3,6] we found no significant relationship between hospital volume and poorer outcomes following RC. It is possible that while our cohort was population-based, the number of RCs performed over the 15 years was fewer than that observed in overseas jurisdictions with larger populations.[3,15] In keeping with our results, one previous Australian study of 804 RC patients reported no significant difference in risk of 30- and 90-day mortalities among high-volume (≥7 RCs/year) versus moderate-volume (4–6/year) and low-volume (≤3/year) hospitals following adjustment for casemix.[8] A further state-based Australian study ($n = 803$ patients), did, however, report a significantly increased risk of in-hospital mortality following RC at low-volume hospitals (<4/year).[9] We conducted additional analyses using various hospital volume categories but found no association between hospital volume and any outcome. The inconsistency in results could be due to differences in patient casemix and/or to heterogeneity in hospital volume categories. However, we did stratify by various casemix variables (including age, stage, co-morbidities, etc.) and found no difference in post-operative mortality across hospital volumes. It should, however, be noted that other patient and disease factors can increase the complexity and risk of poorer outcomes for RC patients and lower volume hospitals may potentially refer higher risk cases to larger tertiary centres.

We found the proportion of RCs performed in higher volume hospitals increased in more recent years with a corresponding decrease in very low-volume hospitals. However, when we stratified by year of surgery, we again found no association between hospital volume and mortality. Could there be other explanations for the lack of a hospital volume outcome relationship in this study? Our study was conducted in Queensland, the most decentralized Australian state where about 40% of the population live outside the state capital.[10] Cancer surgery is routinely performed in larger Queensland regional hospitals and in the case of more complex surgical procedures, experienced surgeons from high-volume hospitals do, where the appropriate clinical and infrastructure support is available, perform these in larger regional hospitals. In the UK, centralization has resulted in a significant decline in the number of RCs performed in low-volume hospitals, and by low-volume surgeons, resulting in a decrease in 30-day mortality.[18] While centralization of RC is not currently a formal policy recommendation in Australia, in Queensland guiding practice statements recommend patients with invasive bladder cancer receive care by a specialist surgical team; are reviewed by a multidisciplinary team; and that facilities performing RCs have intensive care and interventional radiology facilities available.[19] It has been suggested that surgeon volume contributes approximately 40% of the effect of hospital volume on post-operative mortality.[20] In our study, while high-volume surgeons are likely to have also operated in lower volume regional hospitals, we were unable to directly assess this and we acknowledge this is a limitation.

We found risk of post-operative mortality following RC was higher for older patients (≥75 years). In addition, stage at diagnosis and having a positive lymph node(s) were the strongest predictors of 90-day mortality, similar to others when adjustment for patient casemix has been included.[21] Our results highlight the importance of casemix adjustment when examining outcomes following RC and other complex cancer surgeries. Indeed, not adjusting for patient characteristics (such as age, co-morbidities/functional status, etc.) when examining outcomes and quality of surgery restricts our ability to identify potential risk factors relating to those outcomes.

In this study 72% and 56% of patients were alive at 2 and 5 years, respectively, which compares favourably with other studies.[8,22] We observed a survival advantage for patients treated more recently. It is doubtful that the observed improvements are due to patients presenting and being diagnosed at an earlier stage as we found no significant change in stage distribution over time. Rather, improvements in survival for patients treated more recently likely reflects corresponding improvements in surgical techniques and to some extent more frequent use of neoadjuvant and/or adjuvant therapy. We were, however, unable to assess these factors fully in our study. We found later stage (III–IV), positive lymph node(s), no lymph node dissection and surgical margin involvement were all predictors of poorer survival. These findings are in keeping with a large study of 39 000 patients in the USA.[22] In our study, 71% of patients had a lymph node dissection, similar to an English study where approximately 74% of patients received a lymph node dissection.[23] We found the proportion of patients undergoing lymph node dissection increased significantly over time. The number of patients with a positive surgical margin in our study (10%) is also in line with others.[22] We found no association with either 2-year or 5-year survival and hospital volume. While some studies have reported improved survival outcomes for patients treated at high-volume centres,[8,22] results have, however, been inconsistent.[24,25] This inconsistency likely reflects differing methodological approaches (such as lack of adjustment for casemix and in-hospital clustering) as well as heterogeneity of hospital (and surgeon) volumes.

This current study's strength is its population-based nature and the linkage of clinical and administrative data sets. Furthermore, our clinicians conducted a review of all pathology reports for the cohort to extract margin status and details of lymph node dissection. Our study does, however, have some limitations. We were unable to include type or rate of complications, nor type of surgical procedure, which would likely have an impact on factors predictive of post-operative mortality. Additionally, we did not have complete data on neoadjuvant therapy. The absence of surgeon volume in our data is a further limitation.

Conclusions

We observed low post-operative mortality rates overall, with mortality decreasing significantly over time. Some sub-groups of patients experience poorer post-operative outcomes. Appropriate peri- and post-operative care may help to reduce some of the identified differences. Reporting on post-operative outcomes, including survival over time, is important to help monitor progress and identify areas for improvement.

Acknowledgements

We would like to acknowledge the work of the Queensland Cancer Control Analysis Team who maintain the Queensland Oncology Repository and conduct analysis: John Harrington, Nathan Dunn, Danica Cossio and Julie Moore. The members of the Urological Cancer Subcommittee of the Queensland Cancer Control Safety and Quality Partnership are thanked for their ongoing support and advice.

Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Kaplan–Meier 2-year overall survival curves following radical cystectomy.