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Perioperative Mortality and Long-Term Survival after Radical Cystectomy: A Population-Based Study in a Southern European Country on 4,389 Patients

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Keywords
Bladder cancer · Radical cystectomy · Urinary diversion · Lymphadenectomy · Cohort study

Abstract

Purpose: Population-based data on survival after radical cystectomy (RC) are lacking from Southern Europe. The aim of this study was to assess trends and determinants of perioperative mortality and long-term survival in the Veneto region (Northeastern Italy). ***Methods:*** All patients submitted to RC for bladder cancer from January 2004 to December 2016 were identified from the regional archive of hospital discharge records. Age at surgery, gender, comorbidities, hospital volume, calendar period of surgery, and type of urinary diversion were retrieved; vital status and cause of death were obtained by linkage with mortality records. Determinants of 90-day mortality were assessed by multilevel logistic regression; long-term survival was investigated by the Kaplan-Meier method and Cox regression. ***Results:*** Among 4,389 included patients, an increase in the share of patients aged ≥80 years (from 13% in 2004–2008 to 24% in 2013–2016, $p < 0.001$) and a decline in performing continent diversion (from 34.9 to 23.4%, $p < 0.001$) were observed across the study period. Ninety-day mortality did not change over time and was 4% for patients aged <70 years and 13.7% for those aged ≥80 years. Age- and comorbidities-adjusted mortality was significantly lower in hospitals performing >30 RCs/year (odds ratio 0.67, 95% confidence interval 0.48–0.93). At a median follow-up of 67 months, overall survival at 1 year and 5 years was 72 and 40%, respectively, with a higher rate among younger patients treated in high-volume hospitals. ***Conclusion:*** The population of patients treated with RC is rapidly ageing, with a high risk of perioperative and long-term mortality; this changing epidemiological scenario and better outcomes observed in high-volume hospitals support regionalization of the procedure.

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Introduction

Radical cystectomy (RC) represents the gold-standard treatment for patients with muscle-invasive bladder cancer and for those who present with refractory high-grade non-muscle-invasive bladder cancer, as well as an adequate option for salvage purpose after radiotherapy, or to control symptoms in selected patients with advanced disease [1]. RC is a complex and demanding procedure that frequently involves complications resulting in an increased hospital stay and readmission [1], with wide variability in reported postoperative morbidity and mortality [2].

Data on short- and long-term outcomes have typically been reported by single- or multi-center studies. Population-based analyses of administrative and national databases have been published reporting data about patients in the United States [3, 4], Canada [2], Australia [5], and Northern Europe [6]. Lower mortality rates are reported by centers of excellence, with less favorable outcomes registered in population-based studies, especially among older patients [3]. However, data on Southern Europe are almost lacking, with sparse reports limited to in-hospital outcomes [7].

The Veneto region (Northeastern Italy, about 4,900,000 inhabitants) represents an area with a high incidence of bladder cancer [8] in a rapidly ageing population [7]. The aim of the present study was to investigate short- and long-term survival following RC and to assess variation in mortality over time and its association with hospital volume.

Methods

Patients aged ≥18 years undergoing RC in the period 2004–2016 were selected from the archive of hospital discharge records (HDR) of the Veneto region. The archive includes all hospitalizations in regional hospitals, as well as all admissions of residents in Veneto outside the study area; discharge diagnoses and procedures are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). All discharges with a diagnosis of bladder cancer (188.x) and intervention codes corresponding to RC (57.71), other total cystectomy (57.79), and exenteration (68.8) were selected from January 1, 2004, to December 31, 2016. Data on age at surgery (years), gender, year of intervention, presence of comorbidities according to the Charlson Comorbidity Index modification endorsed by the National Cancer Institute [9], and type of urinary diversion (57.87, 57.88 continent, 56.51, 56.71 ileal conduit, 56.61 ureterocutaneostomy) were retrieved. Hospital volume was defined according to the average number of procedures performed each year and classified in 3 classes (<15, 15–30, >30). Notably, in the Veneto region, a center-level volume of 30 cystectomies/year is currently being discussed as the recommended threshold for performing the procedure; sensitivity analysis was carried out with a dichotomized variable for hospital volume, choosing an intermediate cutoff (25 procedures/year).

HDRs data were matched with information recorded in the Regional Archive of Causes of Death to retrieve the vital status on December 31, 2017, and to assess date and cause of death when appropriate. The underlying cause of death (stated on death certificates) was coded according to the ICD-9 until 2006 and according to the ICD-10 from 2007 onward. A death was classified as related to bladder cancer when the underlying cause was cancer of the bladder (ICD-9 188.x, ICD-10 C67.x), neoplasm of unspecified behavior of the bladder (ICD-9 239.4, ICD-10 D41.4), unspecified urologic malignancy (ICD-9 189.9, ICD-10 C68.9), and malignant neoplasm unspecified/multiple primary sites of malignancy (ICD-9 199, ICD-10 C80, C97). Record linkage was performed on electronic health archives previously submitted to an anonymization process assigning to each an alphanumeric code, without any possibility of back-retrieving their identity. Since all analyses were carried out on routinely collected anonymized records, the study was deemed exempt from approval by the local ethical committee.

The association between categorical variables was assessed by the χ^2 test. Short-term mortality was defined as any death that occurred within 90 days after the surgery. Predictors of mortality within 90 days from the procedure were investigated by a multilevel logistic model, to assess the influence of patient-level and hospital-level variables, taking into account the clustering of patients within providers. Kaplan-Meier estimates of observed overall survival at 1 year and 5 years were obtained, and Cox regression was applied to assess factors influencing long-term survival. Relative survival at 5 years was computed by the Ederer II method as the percentage of the observed survival concerning the expected survival in the regional general population of the same age and sex [10]. Predictors for choosing continent diversion were assessed by a Poisson multilevel model. Statistical analyses were carried out with the SAS software version 9.4.

Results

A total of 4,548 residents in the Veneto region underwent RC during the study period. In total, 159 (3.5%) patients were excluded from the analysis: 10 (0.2%) for lack of vital status data and 149 (3.3%) because of referral to facilities outside the Veneto region, without the chance to assign a corresponding hospital volume.

All subsequent analyses were restricted to 4,389 RCs (80.7% males) performed in regional hospitals (Fig. 1). The mean annual number of procedures increased from 314 in 2004–2008 to 366 in 2013–2016, with an increasing share represented by elderly subjects aged ≥80 years (from 13 to 24%, $p < 0.001$). Across the study period, ageing of patients paralleled a decrease in performing continent urinary diversion ($p < 0.001$), a corresponding in-

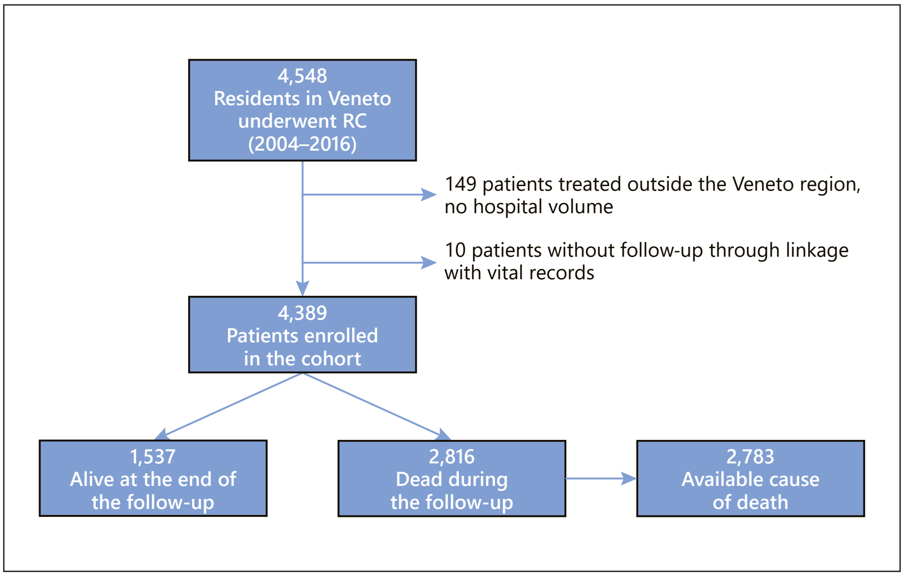

Fig. 1. Selection of study patients and follow-up of the cohort.

Table 1. Patients' characteristics, technique of urinary diversion, and hospital procedural volume by calendar period

	Calendar period			Total
	2004–2008	2009–2012	2013–2016	
All	1,569	1,356	1,464	4,389
Gender				
Male	1,277 (81.4)	1,101 (81.2)	1,164 (79.5)	3,542 (80.7)
Female	292 (18.6)	255 (18.8)	300 (20.5)	847 (19.3)
Age at surgery				
Median (IQR), years	71 (64–76)	72 (65–78)	73 (66–79)	72 (65–78)
<55 years	112 (7.1)	77 (5.7)	80 (5.5)	269 (6.1)
55–59 years	118 (7.5)	83 (6.1)	86 (5.9)	287 (6.5)
60–64 years	205 (13.1)	157 (11.6)	137 (9.4)	499 (11.4)
65–69 years	277 (17.7)	206 (15.2)	229 (15.6)	712 (16.2)
70–74 years	323 (20.6)	305 (22.5)	272 (18.6)	900 (20.5)
75–79 years	325 (20.7)	251 (18.5)	306 (20.9)	882 (20.1)
≥80 years	209 (13.3)	277 (20.4)	354 (24.2)	840 (19.1)
Charlson Comorbidity Index				
=0	1,239 (79.0)	1,184 (87.3)	1,298 (88.7)	3,721 (84.8)
≥1	330 (21.0)	172 (12.7)	166 (11.3)	668 (15.2)
Urinary diversion				
Continent	547 (34.9)	380 (28.0)	343 (23.4)	1,270 (28.9)
Ileal conduit	740 (47.2)	638 (47.1)	696 (47.5)	2,074 (47.3)
Ureterocutaneostomy	177 (11.3)	229 (16.9)	291 (19.9)	697 (15.9)
Missing	105 (6.7)	109 (8.0)	134 (9.2)	348 (7.9)
Hospital volume				
≤15	666 (42.5)	496 (36.6)	420 (28.7)	1,582 (36.0)
15–30	665 (42.4)	577 (42.6)	590 (40.3)	1,832 (41.7)
>30	238 (15.2)	283 (20.9)	454 (31.0)	975 (22.2)

Values are *n* (%) unless otherwise indicated. IQR, interquartile range.

Table 2. Factors associated with continent diversion performed (n = 4,041 with available information)

	RR	95% CI	*p* value
Age at surgery			
<55 years	1		
55–59 years	0.90	0.73–1.11	0.3351
60–64 years	0.69	0.57–0.84	0.0003
65–69 years	0.65	0.54–0.79	<0.0001
70–74 years	0.45	0.37–0.54	<0.0001
75–79 years	0.19	0.15–0.25	<0.0001
≥80 years	0.02	0.01–0.04	<0.0001
Gender			
Male	1.84	1.54–2.20	<0.0001
Female	1		
Charlson Comorbidity Index			
Each 1-point increase (continuous)	0.76	0.66–0.86	<0.0001
Hospital volume			
≤15	1		
15–30	1.31	1.05–1.62	0.0166
>30	1.44	1.08–1.92	0.0131
Calendar period			
2004–2008	1		
2009–2012	0.89	0.70–1.12	0.3235
2013–2016	0.77	0.60–0.98	0.0359

Rate ratio (RR) with 95% confidence intervals (CI) estimated by multilevel Poisson regression.

Table 3. Multiple regression analysis of 90-day postoperative mortality (n = 336)

	90-day mortality, %	OR	95% CI	*p* value
Age				<0.0001
<55 years	2.6	1[a]		
55–59 years	4.9	1.92	(0.76–4.85)	
60–64 years	3.4	1.27	(0.52–3.10)	
65–69 years	4.4	1.62	(0.71–3.74)	
70–74 years	7.9	2.95	(1.34–6.52)	
75–79 years	9.2	3.45	(1.57–7.58)	
≥80 years	13.7	5.54	(2.54–12.08)	
Gender				0.6991
Male	7.7	1.06	(0.79–1.41)	
Female	7.7	1[a]		
Charlson Comorbidity Index				0.0002
=0	6.9	1[a]		
≥1	12.0	1.69	(1.28–2.22)	
Hospital volume				0.0566
≤15	8.6	1[a]		
15–30	7.9	0.88	(0.69–1.13)	
>30	5.7	0.67	(0.48–0.93)	
Calendar period				0.4819
2004–2008	7.5	1[a]		
2009–2012	7.2	0.94	(0.70–1.25)	
2013–2016	8.3	1.11	(0.84–1.48)	

Odds ratios (OR) with 95% confidence intervals (CI) estimated through multilevel logistic regression; C-statistic: 0.667. [a] Reference category.

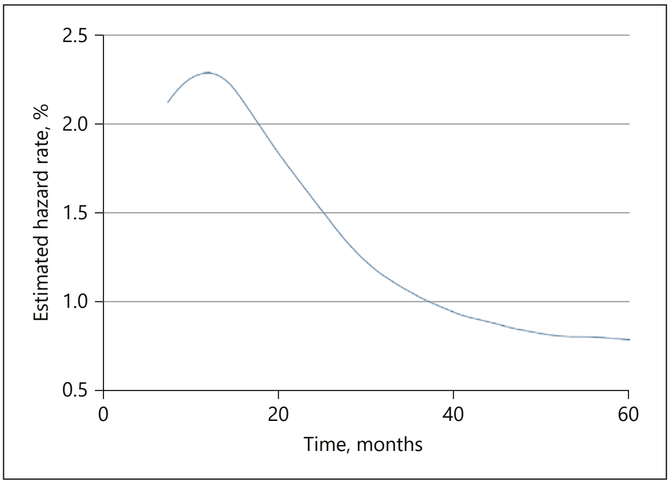

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Fig. 2. Estimated hazard of mortality by months after radical cystectomy.

crease in ureterocutaneostomy, with the proportion of ileal conduit remaining stable (Table 1). Meanwhile, there was a spontaneous shift of patients towards high-volume hospitals. The choosing of continent diversion was higher in younger patients, males, and those without comorbidities, treated in high-volume hospitals (Table 2). After adjustment for these factors, a decrease over the calendar period was confirmed ($p < 0.001$).

At the end of follow-up, 1,573 patients were alive (35.8%), and 2,816 were dead (64.2%); among deceased subjects, the underlying cause was available for 2,783 (98.8%). The cause of death was directly related to bladder cancer in 1,986 patients (71.4%); 453 subjects (16.3%) had a noncancer cause registered, and 344 (12.4%) another neoplasm, mainly lung cancer (3.8%). The proportion of bladder cancer-related deaths was 80.5% in the first year after cystectomy and decreased to 64.3% thereafter. The median follow-up for patients still alive at the end of follow-up was 67.1 months. Mortality at 30 and 90 days from cystectomy was 2.3 and 7.7%, respectively.

Figure 2 reports the monthly risk of death following the procedure. Overall mortality rates remained high through the immediate postoperative period, starting to

Table 4. Overall survival at 1 year and 5 years after radical cystectomy estimated by the Kaplan-Meier method

	n	Deaths, *n* (%)	Kaplan-Meier method		
			1 year (95% CI)	5 years (95% CI)	*p* value, log-rank test
All	4,389	2,816 (64.2)	72.0 (70.7–73.3)	40.3 (38.8–41.8)	
Gender					0.0345
Male	3,542	2,259 (63.8)	72.8 (71.3–74.2)	40.9 (39.2–42.6)	
Female	847	557 (65.8)	68.7 (65.5–71.7)	37.9 (34.4–41.3)	
Age at surgery					<0.0001
<55 years	269	117 (43.5)	83.3 (78.2–87.2)	57.3 (50.8–63.3)	
55–59 years	287	153 (53.3)	82.2 (77.3–86.2)	51.3 (45.0–57.2)	
60–64 years	499	270 (54.1)	81.3 (77.6–84.5)	53.4 (48.8–57.8)	
65–69 years	712	389 (54.6)	80.8 (77.7–83.5)	49.8 (45.8–53.6)	
70–74 years	900	558 (62.0)	74.6 (71.7–77.4)	43.3 (39.9–46.7)	
75–79 years	882	653 (74.0)	67.6 (64.4–70.6)	32.1 (28.8–35.4)	
≥80 years	840	676 (80.5)	53.7 (50.2–57.0)	19.4 (16.5–22.5)	
Charlson Comorbidity Index					<0.0001
=0	3,721	2,300 (61.8)	73.6 (72.1–75.0)	42.2 (40.5–43.9)	
≥1	668	516 (77.3)	63.2 (59.4–66.7)	29.8 (26.2–33.5)	
Hospital volume					<0.0001
≤15	1,582	1,065 (67.3)	70.3 (67.9–72.4)	39.6 (37.1–42.1)	
15–30	1,832	1,230 (67.1)	71.2 (69.0–73.2)	37.6 (35.2–39.9)	
>30	975	521 (53.4)	76.5 (73.7–79.0)	46.9 (43.4–50.3)	
Calendar period					0.0042
2004–2008	1,569	1,162 (74.1)	74.0 (71.8–76.1)	42.5 (40.1–45.0)	
2009–2012	1,356	895 (66.0)	72.2 (69.7–74.5)	40.3 (37.7–42.9)	
2013–2016	1,464	759 (51.8)	69.7 (67.3–72.0)	–	

decline 18 months after RC. The 90-day overall mortality rate was 4% for patients aged ≤70 years and steeply increased in subsequent age classes, reaching 13.7% at ≥80 years. Short-term overall mortality did not change with gender and across calendar periods, whereas the risk of death was reduced by about one-third in high-volume hospitals (Table 3). When hospital volume was modeled as a dichotomous variable (<25 and ≥25 surgeries/year), reduced perioperative mortality in high-volume providers was confirmed (odds ratio 0.74, 95% confidence interval 0.58–0.94, $p = 0.015$, data not shown).

Overall survival was 72.0% at 1 year and 40.3% at 5 years of follow-up; the relative 5-years survival was estimated at 47.2%. 1- and 5-year observed survival was about 80 and 50%, respectively, for patients aged <70 years, thereafter sharply declining with age (Table 4). Observed survival was lower in more recent study years; however, after adjusting for age at Cox regression, no change in survival over time was shown, whereas mortality was significantly lower among patients treated in high-volume hospitals (hazard ratio 0.84, 95% confidence interval 0.76–0.93, $p < 0.001$) (Table 5).

Table 5. Hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality[a] (*n* = 4,389)

	HR (95% CI)[b]	*p* value
Age at surgery		<0.0001
<55 years	1[c]	
55–59 years	1.32 (1.04–1.68)	
60–64 years	1.30 (1.04–1.61)	
65–69 years	1.35 (1.10–1.66)	
70–74 years	1.70 (1.39–2.07)	
75–79 years	2.31 (1.90–2.82)	
≥80 years	3.37 (2.77–4.11)	
Charlson Comorbidity Index		<0.0001
=0	1[c]	
≥1	1.32 (1.20–1.45)	
Hospital volume		0.0002
≤15	1[c]	
15–30	1.04 (0.96–1.13)	
>30	0.84 (0.76–0.93)	

[a] Harrell's C-statistic: 0.611. [b] A stepwise variable selection procedure was applied to the model with a set of candidate predictor variables (gender, age at surgery, Charlson Comorbidity Index, hospital volume, and calendar period). [c] Reference category.

Discussion

The present study, evaluating long-term outcomes in a large cohort of patients undergoing RC, showed an increase in the share of patients aged ≥80 years and a decline in performing continent diversion across the study period. Moreover, 90-day mortality did not change over time, and age- and comorbidities-adjusted mortality was significantly lower in high-volume centers.

There is a lack of homogeneity in short-term mortality reporting after RC mainly due to the outcomes evaluated (in-hospital, 30- or 90-day mortality), study type (single institution, multicenter, population-based), or characteristics of the investigated population. In-hospital mortality among patients treated in 2006–2014 was about 2.2% in the US and 4.6% in Germany [11]; however, this discrepancy might be at least partly due to longer hospital stay in Germany [12].

Overall, mortality rates remain high for several months after the procedure. In a multicenter European study, 30-day mortality was 2.7% and 90-day mortality as high as 9.0% [13]; data from the US National Cancer database confirm the high risk of death between 30 and 90 days of follow-up, with mortality rates of 2.7 and 7.2%, respectively [14]. Similar findings have been reported from Canada [2] and England [6]. Ninety-day overall mortality might, therefore, be a complete measure of the perioperative risk of death but is heavily affected by the age of the treated population. The median age of patients undergoing cystectomy was 69 years in England [6], 68 years in the US, and 69 years in Germany [11]; only 9–10% of patients were aged ≥80 years in New South Wales, Australia [5], and Quebec, Canada [2]. It must be remarked that according to US data from SEER-Medicare Linked Database, 90-day mortality rates steeply increased from 4.4 to 10.1 and 14.8% among patients aged 65–69, 70–79, and ≥80 years, respectively [3]. Short-term mortality registered in the Veneto region is within the range reported from North America and Northern Europe, in spite of a population shifted towards elderly age classes: median age was 72 years, 19% of patients were ≥80 years old, and such figures have been rapidly increasing over time. Data on the stage of the disease, a strong determinant of perioperative mortality, were not available in the current study, and this remains a major limitation of the present report as well as of other studies based on hospital statistics [6, 11]. Nonetheless, international comparisons should be carried out at least separately by broad age groups.

The type of urinary diversion after RC depends mainly on surgeon preferences, tumors, and patient factors. We found that choosing to perform a continent diversion was more frequent in younger patients, males, and those without comorbidities, treated in high-volume hospitals. This finding mirrors both the indication of a continent diversion together with a better quality of life achievable in this part of the population [15–17].

Our findings showed an increase in ureterocutaneostomy from 11% (2004–2008) to currently 20% (2013–2016), which could be attributed solely to the increase in older RC patients (≥80 years from 13 to 24% in the periods mentioned). This trend could be related to the fact that in older patients with a shorter life expectancy the use of the intestine should be avoided in order to reduce major gastrointestinal complications. Both disease-related (advanced tumor stage, positive soft-tissue surgical margins, nonurothelial histology, unresectable tumors, and atypical occult metastasis) and technical factors had the leading role in early mortality after RC [18]. A lower perioperative overall mortality in high-volume hospitals has repeatedly been found in the US, with the effect of hospital volume being stronger compared to that of surgeon volume [4]. In the Netherlands, reduced short-term mortality was found in higher-volume hospitals [19]; in England centralization of radical cystectomies has been paralleled by a decline in 30-day and 90-day mortality [6]. The present report confirms the effect of procedural volume also in a large population-based study carried out in Southern Europe.

Sparse data are available on long-term survival after RC. The observed 5-year survival was 35% in Ontario [20] and 45% in Quebec [2], 48% according to the US National Cancer Database [21], and 53% in New South Wales [5]. Although figures broken down by age group are not usually reported in the literature, data from the Veneto region underline the strong role played by age, comorbidities, and competing causes of death on long-term survival. No improvement over time has been observed; contrasting results have been reported in Northern Europe, with increasing 5-year relative survival after cystectomy being registered in England [22] but not in the Netherlands [19]. An association of long-term survival with hospital volume has consistently been found in the United States [23], Canada [20, 24], Australia [5], the Netherlands [19], and England [22]. Moreover, socioeconomic status-related parameters provide important information on the long-term competing mortality risk after RC supplementary to chronological age and comorbidity [25].

The main limitation of this study is that HDRs contain no cancer-specific data, such as histology, stage, or grade, nor the number of lymph nodes yielded by the RC. Histology and cancer stage have been found to be predictors of postsurgical mortality [26], but grade and stage of disease had a debatable impact on variations in diversions after RC [5, 27, 28]. Moreover, there was no possibility of record linkage to cancer registry data and outpatient treatments archives; consequently, data on the time interval between diagnosis and RC, or prior or adjuvant treatments, such as local therapy or radiotherapy, were not available.

In spite of these limitations, our study findings might be of considerable interest to the general medical community, who need to be aware of contemporary surgical trends, thereby to better advise patients seeking care for surgeries. To the best of our knowledge, the present is the first population-based study reporting perioperative mortality and long-term survival after RC from a large cohort of Southern European patients. Compared with previously published population-based studies [2, 3], we were able to gather data both on patients' urinary diversions and long-term outcomes.

Conclusion

The present findings should be interpreted within the context of a rapidly ageing population of patients affected by bladder cancer, with the associated changes in the surgical approach (e.g., type of urinary diversion) and in the short- and long-term risk of death. Taking into account the high perioperative and long-term mortality among older patients undergoing RC, and better outcomes observed in high-volume hospitals, the present findings support the regionalization of the procedure.

Statement of Ethics

We declare that all subjects have given their written informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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Author Contributions

U.F., A.P., M.C.C., and G.E.C. were responsible for analysis and manuscript writing. W.A., I.S.G., G.E.C., U.F., A.P., M.C.C., and G.N. contributed to project development. U.F., A.P., M.C.C., F.Z., A.P., W.A., and G.E.C. were responsible for manuscript editing. U.F., A.P., and M.C.C. collected all the required data.

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