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EUO Priority Article – Bladder Cancer

The Importance of Hospital and Surgeon Volume as Major Determinants of Morbidity and Mortality After Radical Cystectomy for Bladder Cancer: A Systematic Review and Recommendations by the European Association of Urology Muscle-invasive and Metastatic Bladder Cancer Guideline Panel

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Abstract

Context: In bladder cancer patients treated with radical cystectomy (RC), controversy exists regarding the impact of the annual hospital volume (HV) and/or surgeon volume (SV) on oncological outcomes and quality of care.

Objective: A systematic review was performed to evaluate the impact of HV and SV on clinical outcomes. Primary outcomes included in-hospital, 30-d, and 90-d mortality. Secondary outcomes included complications, long-term survival, positive surgical margin rate, lymphadenectomy performance, length of hospital stay, neobladder performance, and blood loss/transfusion rate.

Evidence acquisition: Medline, Embase, and the Cochrane Central Register of Controlled Trials were searched. Comparative studies published after the year of 2000 including patients who underwent RC for bladder cancer were eligible for inclusion. Partial cystectomy was an exclusion criterion. Risk of bias (RoB) assessment was performed according to the ROBINS-1 tool.

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Evidence synthesis: After screening of 1190 abstracts, 39 studies recruiting 549 542 patients were included. All studies were retrospective observation cohort studies (level of evidence 3). Twenty-two studies reported on HV only, six studies on SV only, and 12 on both. Higher HV, specifically an HV of >10, was associated with improved primary and secondary outcomes in most studies. In addition, there is some evidence that an HV of >20 improves outcomes. For SV, limited and conflicting data are reported. Most studies had moderate to high RoB. The results were synthesized narratively.

Conclusions: Acknowledging the lower level of evidence, HV is likely associated with in-hospital, 30- and 90-d mortality, as well as the secondary outcomes assessed. Based on this study, the European Association of Urology Muscle-invasive and Metastatic Bladder Cancer Guideline Panel recommends hospitals to perform at least 10, and preferably >20, RCs annually or refer the patient to a center that reaches this number. For SV, limited and conflicting data are available. The available evidence suggests HV rather than SV to be the main driver of perioperative outcomes.

1. Introduction

Radical cystectomy (RC) for bladder cancer is a complex urological procedure associated with substantial post-operative morbidity and mortality. Over the years, a number of studies have suggested hospital volume (HV) to be associated with postoperative mortality [1]. As a result, there has been an increasing trend toward centralization of RC [2–6]. In the Netherlands, for example, the Dutch Urological Society has set the quality standard at 20 RCs per year per hospital [7]. Another example is the UK, where a minimum of 50 RCs and/or prostatectomies should be performed according to the Improving Outcomes Guidance guidelines [5]. In spite of these recommendations, a contemporary assessment on the impact of RC volume on mortality, morbidity, and quality of care is still lacking. In addition, although it is tempting to think that more must be better, the question whether threshold RC numbers set by health policy makers is supported by the available literature remains to be answered.

Thus, the aim of this study was to perform a systematic review (SR) of the literature to investigate the impact of HV and/or surgeon volume (SV) on mortality, morbidity, and quality of care parameters. In addition, it was evaluated whether a threshold number of RCs per hospital and/or surgeon can be defined based on the current literature.

2. Evidence acquisition

This SR was undertaken by the European Association of Urology (EAU) Muscle-invasive and Metastatic Bladder Cancer Guideline Panel (EAU MIBC panel). The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and Cochrane handbook principles [8,9]. The study protocol was published a priori (http://www.crd.york.ac.uk/PROSPERO; CRD42018099428).

A specialized librarian (Y.Y.) performed a systematic database search that was complemented by reference list screening. The search was limited to English-language papers and studies published after January 2000. This cutoff was chosen as the HVs and/or SVs prior to 2000 may not reflect current practice in view of increasing centralization reforms [2,5,6]. Conference abstracts and letters to the editor were excluded. Comparative studies, both randomized and nonrandomized, were eligible for inclusion. Registry or database studies were retained, if the analysis was structured as a comparison between control and intervention. The literature search was initiated in June 2018 and updated in February 2019 (Supplementary Fig. 1).

HV/SV was defined as the number of RCs performed per hospital/surgeon per year. If needed, RC volumes were recalculated to an annual RC volume by dividing the total volume of RC performed by the inclusion period. The control group was per definition the lowest-volume group and the intervention groups were numbered by increasing RC volume subgroups. The control and intervention groups per study are reported in Table 1.

Primary outcomes assessed were in-hospital, and 30- and 90-d all-cause mortality after RC. Secondary oncological outcomes included overall survival (OS), recurrence-free survival (RFS), disease-free survival, progression-free survival, cancer-specific survival (CSS), positive surgical margin (PSM) rate, and lymphadenectomy rate. Secondary non-oncological outcomes included blood loss, length of hospital stay (LOS), neobladder rate, and complication rate. In cases of overlapping data (eg, the same database was used with overlapping inclusion periods) for the outcome assessed, either the most comprehensive or the most recent study was retained for analysis.

Abstract screening and full-text screening were performed independently and in duplicate (E.V., V.H., and Y.N.). Risk of bias (RoB) assessment was performed independently using the ROBINS-1 tool [10]. Disagreements or discrepancies were resolved by consensus or arbitration (H.M.B.). In addition to ROBINS-1, the EAU MIBC panel identified five potential confounders: age, tumor stage, body mass index, comorbidity, and (neo-) adjuvant chemotherapy. In studies without adjusted analysis, the relevant a priori defined

Table 1 – Control and intervention groups within the included studies.

No.	Study	Volume	Definition of C and I	C	I1	I2	I3	I4
1	Arora (2019) [11]	Hospital	Chosen	Q1 [a]	Q2 [a]	Q3 [a]	Q4 [a]	
2	Barbieri (2007) [12]	Hospital	Chosen	<3	3–10	11–25	26–50	>50
3	Birkmeyer (2003) [14]	Surgeon	Chosen	<2	2–3.5	>3.5		
4	Bhindi (2014) [13]	Surgeon	No categorical data					
5	Elting (2005) [15]	Hospital	Equal tertiles	<3	4–10	>10		
6	Fairey (2009) [16]	Surgeon	Chosen	<5	5–9	≥10		
7	Goossens-Laan (2010) [6]	Hospital	Chosen	≤5	6–10	>10		
8	Goossens-Laan (2012) [17]	Hospital	Chosen	<10	≥10			
9	Groeben (2019) [18]	Hospital	Chosen	0–3	4–10	11–25	26–50	>50
10	Herr (2004) [19]	Surgeon	Total past 3 yr/mean per year [b]	<50/16.6	50–100/16.6–33.3	>100/>33.3		
11	Hollenbeck (2007) [20]	Hospital	Terciles	<6	6–19	≥20		
12	Khadhouri (2018) [21] [c]	Hospital	Chosen, total past 2 yr	<30	30–60	>60		
		Surgeon	Chosen, total past 2 yr	<9	9–31	>31		
13	Kim (2012) [22]	Hospital	Chosen	<1.5	1.5–5	>5 *		
14	Konety (2005) [24]	Hospital	Terciles	<1.5	1.5–2.75	>2.75		
		Surgeon	Terciles	≤1	1–1.5	>1.5		
15	Konety (2006) [23]	Hospital	Chosen	<1.5	1.5–3	>3		
16	Kulkarni (2013) [25]	Hospital	Quartiles	2.13	4.49	10.45	26.12	
		Surgeon	Quartiles	0.96	2.05	4.44	11.56	
17	Kulkarni (2013) [26]	Hospital	Quartiles	2.13	4.49	10.45	26.12	
		Surgeon	Quartiles	0.96	2.05	4.44	11.56	
18	Leow (2015) [27]	Surgeon	Equal quintiles	1	2	3	4–6	≥7
19	Liedberg (2011) [28]	Hospital	Chosen	<5	5–9	>9		
20	Lin-Brande (2018) [29]	Hospital	Quartiles	1–3	4–7	8–16	17–98	
21	Mayer (2011) [30]	Hospital	Equal tertiles	2–9	10–16	>16		
22	Mayer (2010) [31]	Hospital	Equal tertiles	2–9	10–16	>16		
		Surgeon	Equal tertiles	<5	5–8	>8		
23	McCabe (2007) [32]	Surgeon	Calculated threshold number	<8	≥8			
24	Morgan (2012) [33]	Hospital	Tertiles	<16	16–50	>50		
		Surgeon	Tertiles	<5	6–13	>14		
25	Nimptsch (2017) [35]	Hospital	Equal quintiles	9	18	26	36	57
26	Nielsen (2014) [34]	Hospital	Chosen	0–4	5–9	10–19	20–29	≥30
27	Porter (2011) [36]	Hospital	Mean per tercile	1.76	5.5	18.4		
28	Ravi (2013) [37]	Hospital	Terciles	≤3	4–23	>23		
29	Sabir (2013) [38]	Hospital	Chosen, double the mean	<10	≥10			
30	Santos (2014) [39]	Hospital	Quartiles	5	9.59	17.5	36	
		Surgeon	Quartiles	1.1	1.9	3.4	8.9	
31	Scarberry (2018) [40]	Hospital	Chosen	<10	≥10			
32	Siemens (2014) [41]	Hospital	Quartiles	<4.1	4.1–8.2	8.3–20	>20	
		Surgeon	Quartiles	<1.3	1.3–2.4	2.5–6.2	>6.2	
33	Siemens (2017) [42] [d]	Hospital	Quartiles	Q1	Q2	Q3	Q4	
		Surgeon	Quartiles	Q1	Q2	Q3	Q4	
34	Smaldone (2013) [4]	Hospital	Quintiles	<3	3–4	5–8	9–31	≥32
35	Udovicich (2017) [43]	Hospital	Tertiles	<4	4–10	>10		
36	Vetterlein (2017) [44]	Hospital	Tertiles	<22	22–44	>44		
		Surgeon	Median	<15	≥15			
37	Waingankar (2017) [45]	Hospital	Chosen	<5	5–9	10–19	20–29	≥30
		Surgeon	Chosen	<5	5–9	10–19	20–29	≥30
38	Xia (2018) [46]	Hospital	Quartiles	<5	5–9	10–22	>22	
39	Zakaria (2014) [47]	Hospital	Chosen	<10	10–24	>24		
		Surgeon	Chosen	<5	≥5			

C = control group; I = intervention group; RC = radical cystectomy.
[a] No data on number of RCs within the quartile; RC volume was also presented as a continuous variable.
[b] Number in the last 3 yr of the study period and recalculated per year.
[c] Number in the last 2 yr of the study period and recalculated per year.
[d] Number of patients per quartile was reported, but not case volume per year.

confounders were presented separately in the summary of findings tables.

A narrative synthesis of the results was performed. Descriptive statistics were used to summarize baseline characteristic data. Data from unadjusted and adjusted logistic regression analysis were reported using odds ratios (ORs). For time-to-event data reported by authors using univariable or multivariable Cox regression analysis, data were summarized as hazard ratios (HRs) and 95% confidence intervals (CIs).

3. Evidence synthesis

3.1. *Baseline characteristics of the included studies*

The PRISMA flow diagram is shown in Fig. 1. In total, 39 full-text papers were included [4,6,11–47]. All studies were retrospective database studies (level of evidence [LE] 3). The databases originated from the USA (n = 19), Europe (n = 11), Australia (n = 1), Canada (n = 7), and both the USA and

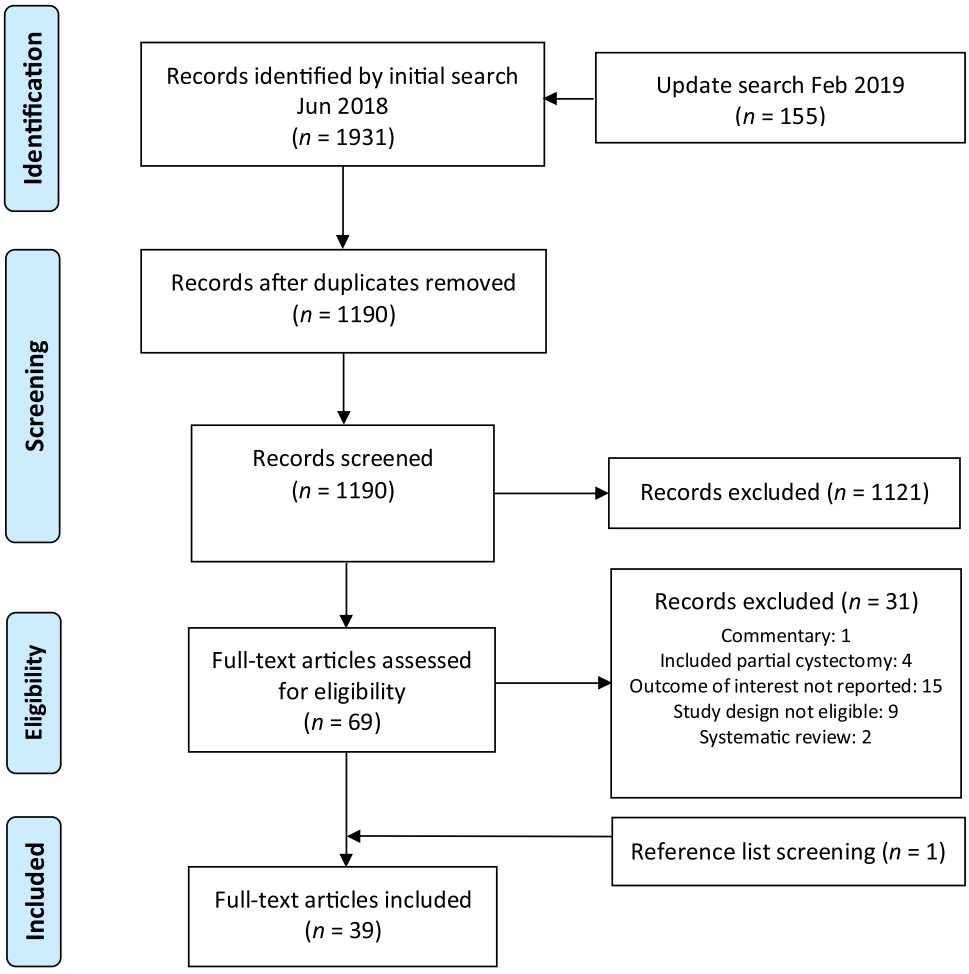

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart.

Germany (*n* = 1). Twenty-one studies reported on HV only, six studies reported on SV only, and 12 studies reported on both. Baseline characteristics of the control and intervention groups are summarized in Table 2.

3.2. *HV: primary outcomes*

Twenty-four studies reported on either of the primary outcomes [4,6,11,12,15,17,18,20,22,24,26,28,30,31,34–38,41,43–45,47].

3.2.1. *In-hospital mortality*

After excluding three studies [20,22,24] with overlapping data, 10 studies were included for analysis (Table 3). All seven studies that performed adjusted analysis reported statistically significantly lower in-hospital mortality rates in hospitals performing more than eight [4], >10 [15,43], 18 [36], >18 [35], >23 [37], and >25 (USA)/>50 (Germany) [18] RCs per year, with ORs ranging from 0.17 to 0.97.

3.2.2. *Thirty-day mortality*

Six studies were included for analysis after exclusion of four [17,30,31,41] overlapping studies (Table 4). In most studies, the absolute 30-d mortality rate was lower in the subgroup of >10 RCs. In addition, Nielsen et al [34] reported a significantly lower mortality rate for >20 RCs compared with 10–20 RCs (OR 0.83) and <10 RCs (OR 0.67) after adjusting for potential confounders.

3.2.3. *Ninety-day mortality*

After excluding one overlapping study [28], seven studies were included for analysis (Table 5). Two studies that performed adjusted analysis reported lower 90-d mortality in hospitals performing >20 RCs (OR 0.77) [34] and >30 RCs [45]. Three other studies reported lower ORs in high-volume hospitals, but failed to reach the level of statistical significance in adjusted analysis [36,44,47].

3.3. *HV: secondary outcomes*

3.3.1. *Complications*

After excluding overlapping studies [22,23,30,39], eight studies were included for analysis (Supplementary Table 1). One study reported on reoperation rates and reported no statistically significant differences [28]. Four studies performed adjusted analysis for risk of complications. Two

Table 2 – Baseline characteristics of the included studies.

	Study	Volume type	Database used	Country	Study period	No. of pts	No. of hospitals	No. of surgeons	Surgical approach (%)
1	Arora (2019) [11]	H	Nationwide Inpatient Sample (NIS)	USA	2008–2011	6790	NR	NR	NR
2	Barbieri (2007) [12]	H	University Health System Consortium Clinical Database	USA	2002–2005	6728	119	NR	NR
3	Bhindi (2014) [13]	S	Toronto Institutional Database	USA	1988–2012	410	2	5	NR
4	Birkmeyer (2003) [14]	S	Medicare Claims Database	USA	1998–1999	6340	NR	2918	NR
5	Elting (2005) [15]	H	Texas Hospital Discharge Public Use Data File	USA	1999–2001	1302	133	NR	NR
6	Fairey (2009) [16]	S	Ontario Database	Canada	1994–2007	523	NR	NR	97.9 open 2.1 lap
7	Goossens-Laan (2010) [6]	H	Netherlands Cancer Registry	NL	2001–2006	29 206	97	NR	NR
8	Goossens-Laan (2012) [17]	H	Netherlands Cancer Registry	NL	1999–2008	2168	97	NR	NR
9	Groeben (2019) [18]	H	NIS and German Billing Database	USA and Germany	2006–2014 [a]	78 158	NR	NR	62.6 open [b] 0.5 lap 1.3 robot 35.6 NR
10	Herr (2004) [19]	S	4 institutional databases	USA	2000–2002	1091	4	16	NR
11	Hollenbeck (2007) [20]	H	NIS	USA	2003	1847	±6000	NR	NR
12	Khadhouri (2018) [21]	H and S	BAUS Electronic Data Registry	UK	2014–2015	3742	84	161	67.8 open 9.1 lap 20.6 robot 2.5 NR
13	Kim (2012) [22]	H	NIS	USA	2001–2008	50 625	1173	NR	NR
14	Konety (2005) [24]	H and S	NIS	USA	1988–1999	13 964	1159	1995	NR
15	Konety (2006) [23]	H	NIS	USA	1998–2002	6577	1057	NR	NR
16	Kulkarni (2013) [25]	H and S	Ontario Database	Canada	1992–2004	2535	90	199	NR
17	Kulkarni (2013) [26]	H and S	Ontario Database	Canada	1992– 2004	3296	90	199	NR
18	Leow (2015) [27]	S	Premier Hospital Database	USA	2003–2010	49 540	NR	NR	97.4 open 2.6 robot
19	Liedberg (2011) [28]	H	Swedish Cancer Registry	Sweden	1997–2002	1126	39	NR	Open
20	Lin-Brande (2018) [29]	H	National Cancer DataBase (NCDB)	USA	2004–2013	27 170	NR	NR	88.2 open 11.8 lap
21	Mayer (2011) [30]	H	Hospital Episode Statistics (HES)	UK	2000–2007	8596	134	346	NR
22	Mayer (2010) [31]	H and S	HES	UK	2000–2007	8596	134	346	NR
23	McCabe (2007) [32]	S	HES	UK	1998–2003	6308	NR	NR	NR
24	Morgan (2012) [33]	H and S	SEER Database	USA	1992–2006	7127	NR	NR	NR
25	Nielsen (2014) [34]	H	NCDB	USA	2004–2011	35 055	1118	NR	NR
26	Nimptsch (2017) [35]	H	DRGS Statistics Database	Germany, Austria, Italy	2009–2014	8706	177	NR	NR
27	Porter (2011) [36]	H	Washington Comprehensive Hospital Abstract Reporting System	USA	2003–2007	823	39	NR	NR
28	Ravi (2013) [37]	H	NIS	USA	1998–2009	79 859	1044	NR	NR
29	Sabir (2013) [38]	H	Swedish Cancer Registry	Sweden	1997–2002	1126	39	NR	Open
30	Santos (2014) [39]	H and S	RAMQ/ISQ Database	Canada	2000–2009	2700	48	122	NR
31	Scarberry (2018) [40]	H	NCDB	USA	2004–2013	39 274	1228	NR	NR
32	Siemens (2014) [41]	H and S	Ontario Database	Canada	1994–2008	2802	NR	NR	NR
33	Siemens (2017) [42]	H and S	Ontario Database	Canada	2000–2008	2593	NR	NR	NR
34	Smaldone (2013) [4]	H	Databay Resources	USA	1996–2009	14 404	411	NR	NR
35	Udovicich (2017) [43]	H	State VictoriaVictorian Admitted Episodes Dataset	Australia	2004–2014	803	18	NR	NR

Table 2 (*Continued*)

	Study	Volume type	Database used	Country	Study period	No. of pts	No. of hospitals	No. of surgeons	Surgical approach (%)
36	Vetterlein (2017) [44]	H and S	Prospective Multicenter Radical Cystectomy Series	Germany, Austria, Italy	2011	679	18	NR	NR
37	Waingankar (2017) [45]	H and S	NCDB	USA	2010–2013	19 346	927	2927	72.1 open 19.9 robot 7.9 lap
38	Xia (2018) [46]	H	NCDB	USA	2006–2013	6551	NR	NR	NR
39	Zakaria (2014) [47]	H and S	RAMQ/ISQ Database	Canada	2000–2009	2778	48	122	NR

H = hospital; lap = laparoscopy; NL = the Netherlands; NR = not reported; pts = patients; S = surgeon; SEER = Surveillance, Epidemiology, and End Results.

[b] Average of the two cohorts.

[a] Radical cystectomy volume analysis was restricted to 2006–2011.

studies reported statistically significantly lower complication rates in hospitals performing >23 [37] and >44 [44] RCs per year. Two studies used the Clavien-Dindo (C-D) classification for complication registration [21,44]. Vetterlein et al [44] reported lower major complication rates (C-D 3–5) in hospitals performing >44 RCs per year than in those performing <22 RCs. In the study by Khadhouri et al [21], no obvious difference in major complications was reported, although the data were suggestive of under-reporting in all subgroups.

3.3.2. *Long-term oncological outcomes*

Six studies reported on long-term oncological outcomes (Supplementary Table 2). All studies, except for the study by Siemens et al [41], reported improved OS for higher-volume hospitals when tested as a categorical variable. When tested as a continuous variable, no statistically significant difference in OS was found in a single study [39]. One study reported RFS [38], which was higher in hospitals performing >10 RCs per year (HR 0.69). The study by Siemens et al [41] was the only study to report on CSS. They reported statistically significantly lower CSS in hospitals performing less than four to eight RCs (HR 1.30) and less than four RCs (HR 1.28) compared with hospitals performing >20 RCs per year.

3.3.3. *Positive soft-tissue surgical margins*

Five studies were included after exclusion of three [25,26,46] overlapping studies (Supplementary Table 3). Sabir et al [38] reported an 8% lower PSM rate in hospitals performing >10 RCs. Scarberry et al [40] also reported a statistically significantly lower PSM rate in hospitals performing >10 RCs (unadjusted OR 0.88, $p <$ 0.01). In both studies, organ-confined disease rates were similar. Performing >20–22 RCs per year, however, does not seem to further improve the PSM rate [41,44].

3.3.4. *Performance of lymph node dissection*

After the exclusion of two studies with overlapping data [25,46], six studies reported on lymph node dissection (LND). Both Sabir et al [38] and Siemens et al [41] reported a 10–20% higher LND rate when >10–20 RCs were performed compared with the performance of eight to 10 RCs (Supplementary Table 4). In both studies, there was no substantial difference in the organ-confined disease rate within the volume categories. One study reported a higher rate of extended LND in hospitals performing >22 and >44 RCs annually compared with hospitals performing <21 RCs (ORs 1.1 and 1.3), but this difference was not statistically significant [44].

3.3.5. *Length of hospital stay*

Ten studies were included after exclusion of two [24,37] duplicate studies (Supplementary Table 5). Eight out of 10 studies reported a shorter LOS in higher-volume hospitals. Three studies performed adjusted analysis [4,20,43]. Hollenbeck et al [20] reported a two-fold decreased risk of prolonged LOS in hospitals performing ≥20 RCs compared with hospitals performing less than six RCs. In contrast, Udovicich et al [43] reported a significantly shorter LOS for

Table 3 – Hospital volume and in-hospital mortality outcomes.

	Study	Control and interventions	In-hospital mortality				Comment
			Rate (%)		Unadjusted analysis	Adjusted analysis	
1	Arora (2019) [11]	C: Q1	2.7		–	–	Hospital volume per quartile not reported
		I1: Q2	1.8				
		I2: Q3	0.8				
		I3: Q4	1.0				
			$p < 0.01$				
2	Barbieri (2007) [12]	C: <3	3.8		–	–	–
		I1: 3–10	2.2				
		I2: 11–25	1.6				
		I3: 26–50	1.4				
		I4: >50	0.5				
3	Elting (2005) [15]	C: <3	2.9		–	Ref	Adjusted for age and comorbidity
		I1: 4–10	2.9			–	
		I2: >10	0.7			OR 0.24 (0.07–0.80), $p = 0.02$	
			$p = 0.04$				
4	Groeben (2019) [18]		USA:	Germany:		USA:	Germany:
		I4: 0–3	3.6	6.7	–	OR 2.26 (1.41–3.62), $p < 0.01$	OR 2.16 (1.37–3.40), $p < 0.01$	Adjusted for surgical approach, urinary diversion, teaching status, size of hospital, gender, age
		I3: 4–10	2.4	5.0		OR 1.51 (1.00–2.28), $p = 0.04$	OR 1.53 (1.20–1.94), $p < 0.01$	
		I2: 11–25	2.6	5.0		OR 1.58 (1.08–2.31), $p = 0.02$	OR 1.22 (1.22–1.81), $p < 0.01$	
		I1: 26–50	1.2	4.1		OR 0.78 (0.47–1.30), $p = 0.34$	OR 1.03 (1.03–1.50), $p = 0.03$	
		C >50	1.5	3.3		Ref	Ref	
			$p < 0.01$	$p < 0.01$			
5	Mayer (2010) [31]	C: 2–9	2.8		–	–	–
		I1: 10–16	3.0				
		I2: >16	2.0				
6	Nimptsch (2017) [35]	C: <9	5.5		Ref	Ref	Adjusted for year of treatment, age, gender, comorbidities, and BMI
		I1: 18	4.9		OR 0.85	OR 0.85 (0.73–0.98)	
		I2: 26	5.0		OR 0.89	OR 0.86 (0.74–1.00)	
		I3: 36	4.4		OR 0.80	OR 0.80 (0.69–0.93)	
		I4: 57	4.0		OR 0.70	OR 0.69 (0.58–0.62)	
7	Porter (2011) [36]	C: mean 1.76	2.5		Ref	Ref	Adjusted for age, gender, discharge year, and number of comorbidities
		I1: mean 5.5	2.8		OR 1.09 (0.33–3.60)	OR 0.99 (0.31–3.19)	
		I2: mean 18.4	1.4		OR 0.53 (0.10–2.78)	OR 0.60 (0.11–3.24)	
8	Ravi (2013) [37]	I2: <4	–		–	OR 1.45 (1.26–1.67)	Adjusted for age, gender, comorbidity, race, insurance status, median income, and urinary diversion type, and year of treatment
		I1: 4–23				OR 2.22 (1.90–2.58)	
		C: >23				Ref	
9	Smaldone (2013) [4]	C: 0–2	4.0		–	Ref	Controlling for year treated, total number of procedures performed, and patient characteristics (age, race, gender, payer group)
		I1: 3–4	3.1			OR 0.75 (0.5–1.1)	
		I2: 5–8	2.8			OR 0.71 (0.5–0.9)	
		I3: 9–31	2.3			OR 0.60 (0.4–0.8)	
		I4: ≥32	1.3			OR 0.33 (0.2–0.5)	
			$p < 0.01$				

Table 3 (*Continued*)

	Study	Control and interventions	In-hospital mortality			Comment
			Rate (%)	Unadjusted analysis	Adjusted analysis	
10	Udovicich (2017) [43]	I2: <4	3.7	OR 4.33 (0.83–22.64), $p = 0.08$	OR 5.74 (1.06–31.20), $p = 0.04$	Adjusted for age, gender, comorbidity, and urinary diversion type
		I1: 4–10	2.5	OR 2.92 (0.64–13.3), $p = 0.16$	OR 3.09 (0.67–14.26), $p = 0.14$	
		C: >10	0.9	Ref	Ref	
			$p = 0.19$			

BMI = body mass index; C = control; I = intervention; OR = odds ratio; Ref = reference.

Table 4 – Hospital volume and 30-d postoperative mortality outcomes.

	Study	Control and interventions	30-d mortality			Comment
			Rate (%)	Unadjusted analysis	Adjusted analysis	
1	Goossens-Laan (2010) [6]	C: ≤5	6.4	Ref	–	No data on the predefined confounding variables was reported
		I1: 6–10	3.6	–		
		I2: >10	1.2	OR 0.2 ($p < 0.01$)		
2	Kulkarni (2013) [26]	C: 2.13	4.3	Per 1 cystectomy:	Per 1 cystectomy:	Adjusted for age, sex, CCI, SES, and admission status
		I1: 4.49	3.7	OR 0.97 (0.94–1.00), $p = 0.09$	OR 0.98 (0.95–1.00), $p = 0.07$	
		I2: 10.45	4.4			
		I3: 26.12	2.9			
			$p > 0.05$			
3	Nielsen (2014) [34]	I2: 0–9	3.2	–	OR 1.5 (1.3–1.9)	Adjusted for age, Elixhauser group, race, income, insurance, tumor stage, prior cancers, neoadjuvant chemotherapy, and year of diagnosis
		I1: 10–19	2.5		OR 1.2 (1.0–1.6)	
		C: ≥20	1.9		Ref	
4	Vetterlein (2017) [44]	C: <22	2.0	Ref	–	No statistically significant differences in age, tumor stage, and BMI among the subgroups Adjuvant chemotherapy not reported Neoadjuvant chemotherapy more frequent in control group Age-adjusted CCI higher in high-volume subgroups
		I1: 22–44	4.3	HR 2.21 (0.56–8.72), $p = 0.26$		
		I2: >44	2.4	HR 1.18 (0.26–5.36), $p = 0.83$		
			$p = 0.41$			
5	Waingankar (2017) [45]	C: <5	3.3	–	2.8 (2.2–3.5) [a]	Propensity scoring; adjusted for age, sex, race, stage, insurance type, median income zip code, surgical approach, WHO grade, lymphovascular invasion, neoadjuvant chemo, Elixhauser comorbid condition, and region of facility
		I1: 5–9	2.9		2.8 (2.1–3.6) [a]	
		I2: 10–19	2.4		2.5 (1.8–3.3) [a]	
		I3: 20–29	2.2		2.4 (1.5–3.2) [a]	
		I4: ≥30	1.9		1.9 (1.4–2.4) [a]	
6	Zakaria (2014) [47]	C: <10	–	–	Ref	Adjusted for age, gender, hospital size and type, and surgeon volume
		I1: 10–24			OR = 0.82 (0.43–1.56), $p = 0.40$	
		I2: ≥25			OR = 1.07 (0.43–2.65), $p = 0.66$	

BMI = body mass index; C = control; CCI = Charlson comorbidity index; I = intervention; OR = odds ratio; Ref = reference; SES = socioeconomic status; WHO = World Health Organization.

[a] Propensity score–weighted cumulative mortality rate.

Table 5 – Hospital volume and 90-d mortality outcomes.

	Study	Control and interventions	90-d mortality			Comment
			Rate (%)	Unadjusted analysis	Adjusted analysis	
1	Nielsen (2014) [34]	I2: 0–9	4.9	–	OR 1.3 (1.1–1.5)	Adjusted for age, Elixhauser group, race, income, insurance, tumor stage, prior cancers, neoadjuvant chemotherapy, and year of diagnosis
		I1: 10–19	5.1		OR 1.2 (1.0–1.4)	
		C: ≥20	3.8		Ref	
2	Porter (2011) [36]	C: mean 1.76	8.4	Ref	Ref	Adjusted for age, gender, discharge year, and number of comorbidities
		I1: mean 5.5	6.9	OR 0.80 (0.36–1.80)	OR 0.77 (0.32–1.84)	
		I2: mean 18.4	5.4	OR 0.62 (0.28–1.40)	OR 0.68 (0.29–1.56)	
3	Sabir (2013) [38]	C: <1	7.0	–	In < pT2:	–
		I1: ≥10	5.0		3%	
			$p > 0.05$		0%	
4	Siemens (2014) [41]	C: <4.1	10	–	–	–
		I1: 4.1–8.2	11			
		I2: 8.3–20	7			
		I3: >20	7			
5	Vetterlein (2017) [44]	C: ≤21	12.8	Ref	Ref	Adjusted for age, age-adjusted CCI, ASA, BMI, smoking status, surgeon case volume, tumor stage, lymph node stage, extranodal extension, concomitant CIS, lymphovascular invasion, and hospital clustering
		I1: 22–44	6.8	OR 0.62 (0.28–1.36), $p = 0.23$	OR 0.62 (0.28–1.36), $p = 0.23$	
		I2: ≥45	4.1	OR 0.30 (0.12–0.73), $p < 0.01$	OR 0.27 (0.03–2.20), $p = 0.22$	
			$p < 0.01$			
6	Waingankar (2017) [45]	C: <5	8.5	–	7.8 (6.7–8.9) [a]	Propensity score by age, sex, race, stage, insurance type, median income, zip code, surgical approach, WHO grade, lymphovascular invasion, neoadjuvant chemo, Elixhauser comorbid condition, and region of facility
		I1: 5–9	8.4		8.0 (6.7–9.2) [a]	
		I2: 10–19	7.2		7.6 (6.2–8.9) [a]	
		I3: 20–29	6.4		7.0 (5.5–8.5) [a]	
		I3: ≥30	5.6		5.5 (4.6–6.3) [a]	
7	Zakaria (2014) [47]	C: <10	–	–	Ref	Adjusted for age, gender, hospital size, hospital type, surgeon volume
		I1: 10–24			OR 0.94 (0.64–1.39), $p = 0.20$	
		I2: ≥25			OR 1.38 (0.79–2.42), $p = 0.15$	

ASA = American Society of Anesthesiologists Classification; BMI = body mass index; C = control; CCI = Charlson comorbidity index; CIS = carcinoma in situ; I = intervention; OR = odds ratio; Ref = reference; WHO = World Health Organization.
[a] Propensity score–weighted cumulative mortality rate.

less than four RCs compared with >10 RCs, although prolonged intensive care admission was more common in the former (63% vs 13%, $p < 0.01$). In these three studies, the reduction in LOS for the highest intervention group and the reference group was approximately 1–3 d. The remaining studies, except for those by Porter et al [36] and Khadhouri et al [21], reported a 2–3-d shorter LOS in high-volume hospitals, although there was no adjustment for case mix. Of interest, the latter study reported that the surgical approach rather than the HV was the main driver of LOS.

3.3.6. *Neobladder performance*

Neobladder performance was reported in five studies (Supplementary Table 6). All studies, except for that by Vetterlein et al [44], reported a statistically significantly higher neobladder rate in hospitals performing more than eight [29], >10 [43], >23 [37], and >50 [33] RCs in unadjusted analysis. The study by Lin-Brande et al [29] was the only study to perform adjusted analysis and reported a 1.86-fold higher neobladder reconstruction rate in the highest intervention group. This study also concluded that high-volume centers with a high volume of open RCs more often perform continent diversion compared with high-volume centers performing predominantly robotic RC.

3.3.7. *Blood loss/transfusion*

Eight studies reported on either blood loss or blood transfusion (Supplementary Table 7). Blood transfusion

Table 6 – Surgeon volume and primary outcomes (in-hospital, 30-d, 90-d mortality).

	Study	In-hospital mortality (%, UVA, MVA)	30-d mortality (%, UVA, MVA)	90-d mortality (%, UVA, MVA)	Comment
1	Birkmeyer (2003) [14]	NR	%: C: 5.5, I1: 5.3, I2: 3.1, $p < 0.01$ [a] 1st MVA (per 1 RC): OR 1.83 (1.37–2.45), $p < 0.01$ [a] 2nd MVA (per 1 RC): OR 1.45 (1.03–2.04), $p < 0.01$ [a]	NR	MVA adjusted for age, sex, race, year of procedure, elective procedure, mean income, type of hospital, hospital location, and teaching status; 2nd MVA also adjusted for hospital volume
2	Khadhouri (2018) [21]	NR	%: C: 1.3, I1: 1.8, I2: 1.4	%: C: 3.2, I1: 2.9, I2: 2.4	
3	Konety (2005) [24]	%: C: 3.9, I1: 3.1, I2: 2.9, $p > 0.05$ MVA: $p > 0.05$ (data not shown)	NR	NR	Additional analysis stratified by age: no statistically significant difference
4	Kulkarni (2013) [26]	NR	%: C: 4.3, I1: 5.1, I2: 3.3, I3: 2.9 UVA (per 1 RC): OR 0.96 (0.90–1.02), $p = 0.17$ MVA (per 1 RC): OR 0.96 (0.90–1.02), $p = 0.14$	NR	Adjusted for age, sex, CCI, SES, and admission status
5	Leow (2015) [27]	NR	NR	%: C: 4.3, I1: 3.7, I2: 2.5, I3: 3.7, I4: 2.4, $p < 0.01$ MVA (1 vs 2): OR 0.84 (0.53–1.33) MVA (1 vs 3): OR 0.56 (0.32–0.96) MVA (1 vs 4): OR 0.83 (0.52–1.34) MVA (1 vs ≥7): OR 0.54 (0.28–1.04)	Adjusted for patient, hospital, and surgical characteristics
6	Mayer (2010) [31]	%: C: 2.8, I1: 2.9, I2: 1.9 UVA (5–8 vs >8): HR 0.67 (0.48–0.95), $p = 0.03$ MVA 1 (5–8 vs >8): HR 0.64 (0.44–0.91), $p = 0.01$ MVA 2 and 3: NS	%: C: 3, I1: 3.2, I2: 2.3	NR	MVA1: adjusted for case mix MVA 2: MVA 1 + clustering of patients within surgeons and surgeons within hospitals MVA 3: MVA 2 + adjustment for structural and process of care variables
7	McCabe (2007) [32]	%: C: 6.7, I: 4.2 Threshold: >8 RCs	NR	NR	
8	Siemens (2014) [41]	NR	%: C: 3, I1: 3, I2: 2, I3: 2	%: C: 11, I1: 9, I2: 8, I3: 6	
9	Vetterlein (2017) [44]	NR	%; C: 3.2, I1: 2.9, $p = 1.00$	%: C: 10.6, I1: 4.7, $p = 0.29$	
10	Waingankar (2017) [45]	NR	%: C: 2.9, I1: 2.2, I2: 2.1,I3: 2.2, I4: 1.8 MVA [b]: C: 2.5, I1: 2.4, I2: 2.1, I3: 2.3, I4: 2.1	%: C: 8.1, I1: 6.9, I2: 6.3, I3: 5.7, I4: 4.0 MVA [b]: C: 7.3, I1: 7.0, I2: 6.8, I3: 5.9, I4: 4.9	Weighted by propensity score: age, sex, race, stage, insurance type, median income, zip code, surgical approach, WHO grade, lymphovascular invasion, neoadjuvant chemotherapy, Elixhauser comorbid condition, and region of facility
11	Zakaria (2014) [47]	NR	MVA (<5 vs ≥5): OR 0.75 (0.42–1.35), $p = 0.35$	MVA (<5 vs ≥5): OR 0.82 (0.57–1.17), $p = 0.29$	Adjusted for age, gender, hospital size, hospital type, and hospital volume

C = control group; CCI = Charlson comorbidity index; HR = hazard ratio; I = intervention group; MVA = multivariate analysis; NR = not reported; NS = not significant; OR = odds ratio; RC = radical cystectomy; SES = socioeconomic status; UVA = univariate analysis.
[a] Operative mortality was defined as either within 30 d or in hospital (even if beyond 30 d).
[b] Propensity scored.

was reported in seven studies. Adjusted analysis, however, was performed in only two studies reporting lower transfusion rates in hospitals performing >10 and >25 RCs [18,43]. Liedberg et al's [28] study was the only study to evaluate blood loss, and found that the number of patients with more blood loss than the median was higher for more than nine RCs (48%) than less than five RCs (29%). It should be noted, however, that this analysis was unadjusted.

3.4. *Surgeon volume*

Eighteen studies reported on SV (Table 2).

3.4.1. *Primary outcomes*

Eleven studies reported on either of the primary outcomes (Table 6). For in-hospital mortality, two studies performed adjusted analysis [24,31]. Mayer et al [31] reported reduced odds of in-hospital mortality for surgeons performing more

than eight RCs per year (vs five to eight RCs per year) when adjusting for case mix. However, when also adjusting for clustering of patients and surgeons as well as process of care variables, SV did not remain independently associated with in-hospital mortality.

One [14] of the four studies [14,26,45,47] that performed adjusted analysis reported statistically significantly higher odds of 30-d mortality for lower-volume surgeons (OR 1.83, $p < 0.01$). When HV was added to the model, SV remained associated with 30-d mortality. Nonetheless, it was calculated that 46% of the effect was attributable to HV.

None of the three studies that performed adjusted analysis reported an association between SV and 90-d mortality. Waingankar et al [45], however, reported a lower 90-d mortality rate for a high-volume surgeon (>30 RCs) in a high-volume hospital (>30 RCs) compared with lower-volume surgeons (<19 RCs) in a high-volume hospital.

3.4.2. Secondary outcomes

Several studies reported on the impact of SV on long-term oncological outcomes [13,16,25,33,39,41,42] with conflicting results. When tested as a continuous variable, Bhindi et al [13] reported no statistically significant OS, RFS, and CSS benefits for higher-volume surgeons, while Kulkarni et al [25] did (HR 0.98). When tested as a categorical variable, Fairey et al [16] found that an SV of five to nine RCs, but not >10, was statistically significantly associated with OS and CSS when compared to an SV of zero to four RCs (OR 0.6). Siemens et al [41] noted that OS was lower in the SV quartile 1–3 compared with the highest SV quartile. Four studies [25,33,39,41] included both HV and SV in their multivariate analysis, with, again, conflicting results. In one study, neither of the volumes remained independently associated with OS. However, in the absence of collinearity between HV and SV, the authors suggested that the benefit of high volume is achieved with either of the volumes [41]. Similar findings were reported by Kulkarni et al [25]. In contrast, Morgan et al [33] found that when both volumes were included in the model, HV remained associated with OS, while SV did not. They concluded that the main driver of long-term outcomes is HV rather than SV. Finally, Santos et al [39] found that both a high HV (Q3/Q4; HR 0.87) and a high SV (Q3/Q4; HR 0.81) were associated with OS. In fact, having surgery in a high-volume hospital and performed by a high-volume surgeon (ie, Q3/Q4) decreased the risk of overall mortality by 20% (HR 0.80, 95% CI: 0.70–0.91).

For complications, Leow et al [27] reported nearly 30% and 45% reduced odds of a major complication (C-D 3–5) for four to six RCs and more than seven RCs, respectively, when compared with one RC. In contrast, Vetterlein et al [44] found that HV, but not SV, was associated with complications after RC.

For PSM and LND, one study [19] was available, which found no difference between these. This study, however, included only tertiary centers with all the surgeons performing at least 15–20 RCs per year. Although not evidence based, in the view of these highly experienced surgeons, a minimum number of 10 RCs per surgeon per year is required to maintain proficiency.

For blood transfusion, Siemens et al [42] reported a higher transfusion rate for first-quartile–volume surgeons (69%) compared with fourth-quartile–volume surgeons (57%; adjusted analysis: OR 1.18, $p < 0.01$).

Konety et al [24] reported a shorter LOS (1.4 d) for a high-volume surgeon (>1.5 RCs) than for a low-volume surgeon (one or fewer RC). This definition of a high-volume surgeon, however, cannot be considered representative in the current era.

3.5. RoB assessment

Most of the studies were deemed to have a moderate to high RoB, as summarized in Supplementary Table 8.

3.6. Discussion

HV and/or SV is thought to be related to the outcome RC, which is considered the urological operation associated with one of the highest complication and mortality rates. Outcome, in this case, can be survival at different time points, but also complication rates and potential quality criteria (eg, performance of LND or neobladder reconstruction). In some countries, a minimal number of cystectomies have been set as a quality standard, resulting in centralization of this procedure. This suggests that there is convincing literature supporting a certain threshold number, or the other way around, that a certain threshold number has been shown to improve outcomes after its introduction. It sounds reasonable to suggest that higher volumes result in better outcome, for example, due to the availability of a dedicated multidisciplinary infrastructure and expertise in the perioperative care process. Hollenbeck et al [20] noticed clear differences in perioperative care between high- and low-volume hospitals, and attributed 23% of the volume-outcome relationship to these differences. Nonetheless, high-level evidence relating volume to outcome after RC is lacking. Therefore, the EAU MIBC panel conducted an SR looking at the impact of HV and/or SV on several outcome measures. Furthermore, the panel discussed whether a minimal threshold number of RCs per hospital and/or surgeon could be defined based on the findings of this SR.

3.6.1. Principal findings

In spite of the lower LE of the included studies, this SR, including 39 database studies and 549 542 patients, shows that there is substantial evidence that HV is associated with the primary and secondary outcomes assessed. For SV, in contrast, the evidence base is limited and conflicting. Some studies have evaluated the impact of both HV and SV. For example, Mayer et al [31] reported a higher SV to be associated with lower in-hospital mortality after adjustment for case mix. However, when also adjusting for clustering of patients and surgeons as well as process of care variables, SV did not remain independently associated with in-hospital mortality. This finding is not completely surprising, as it is also the personal belief of the expert panel that RC is a multidisciplinary effort and that the "total package" of care determines the final outcome. This package

includes not only the surgeon, but also the anesthesiology team [48], intensive care unit, and treating team at the ward.

The subsequent question is: "what is considered a high-volume hospital?" Obviously, the definition of "high volume" differed substantially among the 40 studies included. Konety et al [24], for example, considered >2.75 RCs per year as high volume, whereas Nimptsch and Mansky [35] set the bar at 57 RCs per year. Although these are the extremes and these studies were published 12 yr apart, this illustrates the differences in the interpretation of high volume. Another complicating factor is the differences between the USA and Europe. In the USA, there are very-high-volume centers (>50), but also centers that perform only a few cystectomies per year, whereas in Europe there are fewer outliers. This was demonstrated by Groeben et al [18], who compared data from both the USA and Germany over the years 2006–2011. In the USA, 12.7% of RCs were performed in hospitals performing zero to three RCs and 23.1% in hospitals performing four to 10 RCs, as compared with 1.0% and 10.0%, respectively, in Germany. In contrast, in the USA, 26.6% of RCs were performed in hospitals performing >50 RCs, as compared with 13.6% in Germany. In short, it is better to refrain from using the terms low and high volume, but simply mention the number of procedures performed.

Defining an evidence-based threshold number of HV proved daunting. First, the LE of the included studies was rather low. However, it is not anticipated that a study with higher LE will be performed in the near future, if at all possible. Second, there are a number of potential confounding variables that may have impacted the primary and secondary outcomes. In the tables, all variables that were adjusted for in the analyses are presented. In the data analysis process, it was taken into account whether studies had been corrected for potential confounders (including the a priori identified confounding variables) by performing RoB and risk of confounding analysis using the ROBINS-1 tool. Careful analysis of the 30-d mortality data, as one of the primary outcomes, showed a consistent drop in hospitals performing >10 RCs per year (Table 4). Most of the included studies had at least been corrected for age and comorbidity/performance status, which were among the important confounders identified a priori. A similar observation was made for in-hospital mortality (Table 3). In addition, data in some studies suggest a further reduction of in-hospital/30-d mortality when >20–30 RCs were performed. One study attempted to calculate a threshold number [35]. In this study, a Benders' value of acceptable risk limit was defined, which estimates a minimum volume threshold to achieve a risk of in-hospital mortality that is lower than a predefined acceptable risk. They found that a threshold number of 31 RCs was required for the in-hospital mortality to fall below 4.7%, which was defined as the acceptable risk.

In general, most studies reported improved secondary outcomes when >10–20 RCs per year were performed. Examples include the rate of LND, which was on average 10–20% higher in hospitals performing >10–20 RCs per year. In addition, the two studies that evaluated the surgical margin status both reported a lower positive margin rate for HV >10 RCs [38,40]. Furthermore, Lin-Brande et al [29] reported a 1.44-fold increased likelihood of neobladder reconstruction in hospitals performing eight to 16 RCs as compared with hospitals performing fewer RCs. The likelihood was even higher (1.86-fold) in hospitals performing >17 cases per year.

Collectively, the available data suggest a substantial improvement in primary and secondary outcomes when >10 RCs are performed per hospital per year. Possibly, the outcomes may be even better in hospitals performing >20 RCs. The panel concluded that the minimum recommended number of RCs per hospital per year is 10, but that hospitals should strive to perform >20 RCs as this might further improve outcomes. For SV, the evidence base is limited and conflicting, and no clear recommendation on a number can be made.

3.6.2. *Implications for clinical practice and further research*

In a previous SR by Goossens-Laan et al [1] in 2011, the inverse relationship between volume and in-hospital and/or 30-d mortality was reported. The current SR, however, differs in several ways. First of all, compared with their SR that was published 8 yr ago, this SR includes a larger number and more contemporary studies aligning better with current practice. In addition, important secondary endpoints addressed in this review were not taken into account in the analysis of their review. Finally, the authors did not consider it feasible to identify a minimum volume threshold from the included studies.

When setting a minimal volume, several issues need to be considered. First of all, minimum volume standards do not take geographical spread into account and can cause logistic and financial problems. Furthermore, in the current era, we also have to address robot-assisted RC (RARC) in this discussion. The volume discussion may even be of greater importance for RARC as it is associated with a long learning curve. A study by the International Robotic Cystectomy Consortium determined that 21 patients were needed for an institution to achieve a prespecified operative time threshold and >30 patients were needed to have a PSM rate below 5% [49]. They even found improvement in surgeon performance beyond 50 cases. A more recent review by Moschini et al [50] confirmed that surgical volume appeared to be related to the improvement of perioperative outcomes and complications after RARC. With increasing world-wide experience, more data on the RARC volume-outcome relationship will become available. Nonetheless, regardless of the surgical approach used, the results of this study underscore the potential benefits of centralization of bladder cancer care, and it is recommended for hospitals to seek collaborations with neighboring hospitals. Moreover, recent developments in the perioperative management such as enhanced recovery after surgery (ERAS) may also impact the perioperative outcomes [51]. Yet, as none of the included studies reported on ERAS, no recommendation could be made in the current study.

3.6.3. Limitations and strengths

The major strength of this review is the use of robust and comprehensive methodology, and contemporary data. Notwithstanding the limited LE, this study contains data of more than 500 000 unique patients from countries all over the world. This "real-world data" are the best we currently have, and it is highly unlikely that a randomized clinical trial in this setting will ever be conducted. Another limitation is the lack of subgroup analyses, which we planned a priori. Unfortunately, due to the lack of specified data, these subgroup analyses (eg, neoadjuvant chemo and salvage procedures) could not be performed.

4. Conclusions

Acknowledging the lower LE, HV is likely associated with in-hospital, 30-d, and 90-d mortality as well as the secondary outcomes assessed. Based on this study, the EAU MIBC panel recommends hospitals to perform at least 10, and preferably >20, RCs annually or refer the patient to a center that reaches this number. For SV, limited and conflicting data are available. The available evidence suggests HV rather than SV to be the main driver of perioperative outcomes.

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Appendix A. Supplementary data

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