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The effect of hospital caseload on perioperative morbidity and treatment-related costs in patients undergoing radical cystectomy

Der Effekt des Krankenhaus-Caseloads auf die perioperative Morbidität und behandlungsassoziierte Kosten bei der radikalen Zystektomie

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1. Abbreviations

BCG: Bacillus Calmette-Guérin

CCI: Comprehensive Complication Index

CI: Confidence Interval

CIS: Carcinoma In Situ

EAU: European Association of Urology

G1: Grade 1

G2: Grade 2

G3: Grade 3

GRAND: German Nationwide Inpatient Data

ICD-10-GM: International Statistical Classification of Diseases and Related Health Problems, 10th revision, German modification

NIS: Nationwide Inpatient Sample

OPS: Procedure Classification (*Operationen- and Prozedurenschlüssel*)

OR: Odds Ratio

PUNLMP: Papillary Urothelial Neoplasm of Low Malignant Potential

RC: Radical Cystectomy

RCT: Randomized-Controlled Trial

ROC: Receiver-Operating-Characteristics

SD: Standard Deviation

TUR-B: Transurethral Resection of the Bladder tumors

USA: United States of America

WHO: World Health Organization

2. Zusammenfassung

Die aktuellen Leitlinien der Europäischen Gesellschaft für Urologie empfehlen, dass Krankenhäuser jährlich mindestens zehn, vorzugsweise aber mehr als zwanzig RC durchführen, um akzeptable perioperative Ergebnisse zu erzielen. Dennoch ist die optimale jährliche Fallzahl für die RC nach wie vor unbekannt. Daher haben wir uns zum Ziel gesetzt, einen evidenzbasierten Schwellenwert für das optimale jährliche RC-Krankenhausvolumen zu ermitteln und dessen klinische Bedeutung anhand der wichtigsten perioperativen Ergebnisse (Mortalität, Morbidität, Verweildauer und behandlungsassoziierte Kosten) zu bewerten. Auf der Grundlage der DRG-Datenbank, der vom Forschungsdatenzentrum des Statistischen Bundesamtes für die Jahre 2005 bis 2020 zur Verfügung gestellt wurde (Antrag: LMU - 4710-2022), wurde durch ROC-Analysen ein optimaler jährlicher Schwellenwert für das Krankenhausvolumen definiert. Die DRG-Datenbank enthält alle vergüteten stationären Fälle Deutschlands mit Ausnahme der psychiatrischen, forensischen und militärischen Fälle. Alle Daten sind im Forschungsdatenzentrum des Statistischen Bundesamtes anonymisiert gespeichert. Alle Krankenhäuser sind verpflichtet, Patientendaten zu stationären Diagnosen, Begleiterkrankungen sowie perioperativen Ergebnissen und operativen Eingriffen zu verschlüsseln und an das Institut für das Entgeltsystem im Krankenhaus zu übermitteln. Diese Daten sind für alle deutschen Krankenhäuser verpflichtend, um ihre entsprechende Vergütung zu erhalten. Die Diagnosen und perioperativen Ergebnisse werden nach dem ICD-10-GM verschlüsselt und die chirurgischen Eingriffe nach dem deutschen OPS. Auf der Grundlage der ROC-Analysen wurde der optimale jährliche Schwellenwert für das Krankenhausvolumen, in Bezug auf Mortalität, Ileus, Sepsis, Transfusion, Verweildauer und behandlungsassoziierte Kosten, bei 54, 50, 44, 44, 71 und 76 RC/Jahr bestimmt. Deswegen wurde der jährliche Schwellenwert von 50 RC/Jahr und 70 RC/Jahr, sowie der vorgeschlagene von den europäischen Leitlinien (20 RC/Jahr) verwendet, um multiple Analysen auf Patientenebene durchzuführen. Insgesamt wurden 95,841 Patienten eingeschlossen. Davon wurden 28,291 Patienten (30 %) in Krankenhäusern mit niedrigem (<20 Fälle/Jahr), 49616 (52 %) in Krankenhäusern mit mittlerem (20-49 Fälle/Jahr) und 17,934 (19 %) in Krankenhäusern mit hohem Caseload (≥50 Fälle/Jahr) in Deutschland behandelt. Multivariaten Analysen zeigten, dass Patienten, die in High-Caseload-Krankenhäusern operiert wurden, mit einem statistisch signifikant niedrigeren Mortalitätsrisiko (OR: 0,72, 95% CI: 0,64 bis 0,8, $p < 0,001$) im Vergleich zu Patienten, die in Low-Caseload-Krankenhäusern operiert wurden, verbunden waren. Dazu wurden die Kosten um 457 Euro (95% CI: 207 bis 707, $p < 0,001$) und die Verweildauer um 2,7 Tage (95% CI: 2,4 bis 2,9, $p < 0,001$) nach RC in High-Caseload-Krankenhäusern reduziert. Interessanterweise traten bei Patienten, die in Low-Caseload-Krankenhäusern operiert wurden, mehr perioperative Komplikationen (Transfusionen, Ileus und Sepsis) auf. Darüber hinaus war der Schwellenwert von 70 Fällen/Jahr auch mit besseren perioperativen Ergebnissen (Mortalität, Morbidität, Verweildauer und Kosten) verbunden. Die Zentralisierung der RC scheint nicht nur die Morbidität und die Mortalität zu verbessern, sondern auch die Verweildauer und die behandlungsassoziierten Kosten. Auf der Grundlage der Analysen sollten Krankenhäuser mit mindestens 50 RC/Jahr als Referenzzentren und Krankenhäuser mit mindestens 70 RC/Jahr als Exzellenzzentren betrachtet werden. Krankenhäuser mit weniger als 10 RC/Jahr sollten Patienten an andere Zentren überweisen.

3. Abstract

The European guideline recommendations on bladder cancer suggest that hospitals should perform at least ten, and preferably more than twenty RC per year, to achieve acceptable perioperative outcomes. Still, the optimal annual caseload volume for RC remains unknown. Thus, the present dissertation aimed to determine an evidence-based optimal annual RC hospital volume threshold and to evaluate its clinical significance based on major perioperative outcomes (mortality, morbidity, length of hospital stay, and hospital revenues). Based on the DRG dataset provided by the Research Data Center of the Federal Bureau of Statistics from 2005 to 2020 (agreement: LMU - 4710-2022), an optimal annual hospital volume threshold was defined through ROC analyses. The DRG dataset contains all reimbursed inpatient cases in Germany apart from psychiatric, forensic, and military cases. All data are available and stored anonymized at the Research Data Center of Federal Bureau of Statistics. All hospitals are required to code and transfer to the Institute for the Hospital Remuneration System patient data on inpatient diagnoses, coexisting conditions, as well as on perioperative outcomes, and surgical procedures. These data are mandatory for all German hospitals to receive their corresponding remuneration. These diagnoses and perioperative outcomes are coded according to the ICD-10-GM, whereas surgical procedures are coded according to the German OPS. Based on these ROC analyses, the optimal annual hospital volume threshold for RC that reduces mortality, ileus, sepsis, transfusion, hospital stay, and costs was determined by 54, 50, 44, 44, 71, and 76 RCs/year, respectively. Thus, both the annual threshold of 50 and 70 cases/year and the annual threshold of 20 cases/year as proposed by the European recommendations on bladder cancer were used to perform multiple analyses on a patient level. Overall, 95,841 patients were included. Of them, 28,291 (30%) underwent RC in low- (<20 cases/year), 49,616 (52%) in intermediate- (20-49 cases/year), and 17,934 (19%) in high-volume (≥50 cases/year) hospitals in Germany. After adjusting for major determinants, patients undergoing surgery in high-volume hospitals were associated with statistically significant lower risk for mortality (OR: 0.72, 95% CI: 0.64 to 0.8, $p < 0.001$) compared to patients undergoing surgery in low-volume hospitals. Moreover, the costs were reduced by 457 euros (95% CI: 207 to 707, $p < 0.001$) and the length of hospital stay by 2.7 days (95% CI: 2.4 to 2.9, $p < 0.001$) after RC in high-volume hospitals.

It should be highlighted that patients that underwent surgery in low-volume hospitals developed more perioperative complications (transfusion, ileus, and sepsis). Furthermore, the threshold of 70 cases/year was also associated with improved perioperative outcomes (mortality, morbidity, hospital stay, and costs). The centralization of aggressive bladder cancer care seems to not only improve morbidity and mortality but also to reduce both the length of hospital stay and hospital revenues. Based on the present analyses, hospitals that perform at least 50 RCs/year should be considered referral centers, hospitals that perform at least 70 RCs/year should be considered excellence centers and hospitals that perform less than 10 RCs/year should refer patients to other centers.

4. Introduction

4.1 Epidemiology

Bladder cancer is considered among the commonest cancer types worldwide, accounting for approximately 550,000 new cases every year [1]. It is responsible for about 200,000 deaths every year [2]. According to estimates of the Robert Koch Institute, approximately 28,000 people are diagnosed with bladder cancer and 6,000 people die from bladder cancer every year in Germany [3]. It is considered the second most common urological malignancy after prostate cancer [4]. Nevertheless, its incidence and mortality rates widely differ worldwide due to differences in risk factors, diagnostic procedures, and variations in access to the medical healthcare system. Bladder cancer mainly affects the elderly with a median age at diagnosis of about 73 years [2], posing an important burden to both the patients and the healthcare system [5]. The risk of developing bladder cancer before 70 years of age is about 2% for men and 0.5% to 1% for women [6].

In Germany, bladder cancer is considered the fourth most common tumor in men and the 14th most common tumor in women. Overall, men are diagnosed about three times more often than women [7]. The age-standardized yearly incidence of bladder cancer is about 18 cases per 100,000 men and 4.5 cases per 100,000 women. Accordingly, its age-standardized yearly mortality rate is about 3 deaths per 100,000 men and 1 death per 100,000 women [8]. In about 75% of the cases, bladder cancer is diagnosed in a non-muscle invasive stage at the time of initial diagnosis. Interestingly, considering that common symptoms of urinary bladder cancer include macrohematuria, pollakiuria, or dysuria and given that these symptoms may be often attributed to urinary tract infections (commoner in women), bladder cancer is diagnosed in 40% of cases in a muscle-invasive stage at the time of initial diagnosis in women [9].

4.2 Etiology

Even though the incidence of urinary bladder cancer remains relatively stable in Germany through the last few years, there are plenty of risk factors that have been related to bladder cancer. Smoking is the most important risk factor, accounting for about 50% of all cases [10]. The aromatic amines and polycyclic aromatic hydrocarbons within the tobacco smoke are excreted from the kidneys and cause damage to the urothelium leading to the development of bladder cancer. The risk of bladder cancer increases with smoking duration and intensity and is, therefore, measured in packyears [11]. Passive exposure to tobacco smoke also increases the risk of bladder cancer. Interestingly, patients with bladder cancer that continue smoking after diagnosis have an increased risk of regression and progression compared to patients that quit tobacco smoking after the diagnosis of bladder cancer [12].

Occupational exposure to aromatic amines and hydrocarbons is considered the second most important risk factor, accounting for about 10% of all bladder cancer cases. Occupational exposure affects predominantly workers in the paint, dye, metal, or petroleum industry. However, due to improved occupational health precaution measures in developed industrial settings and work-safety guidelines, the new cases of occupational-related bladder cancer are steadily decreasing [13]. Both schistosomiasis and exposure to pelvic ionizing radiation are also associated with an increased risk of bladder cancer [14,15].

Furthermore, chemotherapy seems to increase the risk of urinary bladder cancer. This typically includes the cytostatic drug cyclophosphamide. However, concomitant prophylactic administration of MESNA (sodium 2-mercaptoethanesulfonate) neutralizes the responsible toxic metabolite, acrolein, and renders cyclophosphamide harmless to the urothelium [16]. Of note, positive family history may only have little impact on the development of bladder cancer. The higher incidence of bladder cancer reported in first- and second-degree relatives of patients with positive family history seems to be attributed to common exposure to other known risk factors, such as tobacco [17]. Accordingly, dietary habits and environmental factors play only a limited role in the development of bladder cancer. Moreover, the available evidence is inconclusive about the role (positive or negative) of other risk factors such as vitamin D, different types of diet (Western, Mediterranean), and alcohol consumption [18].

4.3 Pathological staging and classification

Pure urothelial carcinoma is by far the most common bladder cancer type accounting for over 90% of all cases [19,20]. Nevertheless, the diagnosis of histological variants of bladder cancer has increased during the last few years. The latter is attributed to the awareness and improved reporting of pathologists, the involvement of genitourinary pathologists, as well as to the recent advances in immunohistochemical techniques [21]. Based on their morphological characteristics, histological variants of bladder cancer are subclassified into urothelial and non-urothelial subtypes [22]. Urothelial variants display urothelial differentiation mixed with specific morphological phenotypes (squamous or glandular differentiation, plasmacytoid, micropapillary, sarcomatoid), whereas non-urothelial variants exhibit independent features (adenocarcinoma, squamous cell carcinoma, or neuroendocrine variants) [23].

Primary tumors of the urinary bladder that are confined to the mucosa are classified as Ta, while those invading the lamina propria are classified as T1. Intraepithelial, high-grade tumors confined to the mucosa are classified as carcinoma in situ (Tis). Tumors invading the tunica muscularis and the detrusor muscle are classified as T2, while those invading surrounding tissues are classified as T3 (perivesical tissue) and T4 (other structures such as prostate, uterus, pelvic or vaginal wall). Accordingly, the regional lymph node metastases are subclassified based on their number and their positivity [24]. The latest TNM classification proposed by the Union International Contre le Cancer is presented in Table 1.

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
	T2a Tumour invades superficial muscle (inner half)
	T2b Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
	T3a Microscopically
	T3b Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina pelvic wall, abdominal wall
	T4a Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b Tumour invades pelvic wall or abdominal wall
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
M0	No distant metastasis
	M1a Non-regional lymph nodes
	M1b Other distant metastases

Table 1: The latest TNM classification proposed in 2017 by the Union International Contre le Cancer (UICC).

In 2004, the WHO published a histological classification system for non-muscle invasive bladder cancers, subclassifying them, based on their differentiation and, in turn, to their prognosis, to papillary urothelial neoplasm of low malignant potential (PUNLMP), low- and high-grade papillary carcinoma [25]. This system provides a different risk stratification compared to the older 1973 WHO classification, which subclassified non-muscle invasive urothelial cancer to G1, G2, and G3 categories [26]. Both the 2004 and the 1973 WHO classifications display similar prognostic values [27]. Importantly, all variant histology tumors are considered G3 high-grade. It should be also noted that there is important interobserver and intraobserver variability among pathologists for the diagnosis of both CIS (agreement in about 75% of cases) and WHO grading (agreement in about 55% of cases) [28].

4.4 Symptoms

Bladder carcinoma is often characterized by painless macro- or microhematuria. Macrohematuria is associated with a higher stage at diagnosis compared to microhematuria. In patients with confirmed bladder cancer, macrohematuria is observed in about 78% of all cases and microhematuria in 14% of all cases. On the contrary, no erythrocytes in the urine are detected only in 8% of all cases, [29]. Other symptoms of bladder cancer include dysuria and pollakiuria. These symptoms are particularly common in patients with CIS. In advanced stages, urinary bladder carcinoma may become symptomatic with obstruction of the upper urinary tract or urinary retention, with flank pain or B-symptoms (weight loss, fever, or night sweats). In metastatic disease, symptoms from the system with metastases are also common (e.g. musculoskeletal pain, respiratory problems, neurological deficit) [30].

4.5 Diagnosis

Targeted patient history and physical examination are always important during the assessment of patients with bladder cancer. Ultrasound should be performed as an adjunct to clinical examination as it can detect multiple abnormalities of the upper- and lower urinary tract, including bladder cancer (with low sensitivity) [31]. Nevertheless, outpatient cystoscopy (flexible or rigid) is the basic pillar in the diagnosis of bladder cancer, since it allows the assessment of the urethra, prostate, urinary bladder, and ureteral orifices [32]. Especially in men, the use of a flexible cystoscope is recommended due to the male anatomy, given that it is associated with better patient comfort without compromising effectiveness. During cystoscopy, the urinary bladder is thoroughly examined, the tumor can be localized and measured, urine cytology can be obtained, and the tumor may be also biopsied [33]. The findings of the cystoscopy display low interobserver agreement with a sensitivity of 80% and a specificity of 90% for bladder tumors. Tumors that can be missed include predominantly small papillary carcinomas and CIS [34].

Computed tomography urography is also implemented for the diagnosis and staging of tumors in the upper and lower urinary tract. Alternatively, in patients with contraindications for computed tomography urography, a multi-parametric magnetic resonance imaging can be performed [35].

Urine cytology is also an integral part of bladder cancer diagnosis as it displays high sensitivity for high-grade tumors (84%), but low sensitivity for low-grade tumors. Furthermore, its sensitivity for CIS displays wide variability (28–100%) [36]. Cytology can be taken both from the urinary bladder and from the upper urinary tract. Positive voided urinary cytology indicates the presence of urothelial cancer anywhere in the urinary tract, while negative cytology does not exclude it. Cytological interpretation displays also interobserver and intraobserver variability. In an attempt to facilitate its interpretation, the Paris System, which was lastly updated in 2022, defines urinary cytology categories as follows [37]:

- No adequate diagnosis possible
- Negative for urothelial cancer
- Atypical urothelial cells
- Suspicious for high-grade urothelial cancer
- High-grade urothelial cancer

Considering the low sensitivity of urine cytology in low-grade tumors, numerous urinary tests and urinary molecular markers have been developed for the diagnosis and follow-up of urinary bladder cancer [38,39]. Still, none of these tests has yet found its way through the clinical pipeline [40].

4.6 Management of non-muscle invasive bladder cancer

Bladder cancer is diagnosed in about 75% of the patients in a non-muscle-invasive stage and is managed by TUR-B with or without adjuvant intravesical immunotherapy or chemotherapy based on the patient's characteristics and the stage of the tumor [41–43]. The goals of TUR-B in the non-muscle invasive stage are to establish the diagnosis, to stratify the risk of tumor, and to completely remove all visible lesions [44].

Patients who are diagnosed with non-muscle-invasive bladder tumors display a 5-year recurrence rate of 31% to 78% and a 5-year progression rate of 0.8% to 45%, depending on tumor and patient characteristics [45]. To facilitate clinical decision-making, it is recommended to stratify patients with bladder tumors into risk groups based on their risk of progression to muscle-invasive disease [46]. To date, the 2021 EAU NMIBC scoring model is widely used for this purpose. It takes into consideration the grading of the tumor (either WHO 1973 or WHO 2004), the patient’s age (under or over 70), the number of tumors (single or multiple), the diameter of the tumor (under or over 3 cm) and the presence of concomitant CIS. Low-risk patients display a 5-year progression rate of 0.6% to 0.9%, moderate-risk patients display a 5-year progression rate of 4% to 5%, high-risk patients display a 5-year progression rate of 10% to 11%, whereas very high-risk patients display a 5-year progression rate of 40% to 44% [47].

After complete tumor resection, active surveillance is recommended for low-risk tumors in the long term. Patients with low-risk tumors require cystoscopy at three months. If negative, a subsequent cystoscopy is recommended nine months later, and thereafter, yearly for a total follow-up duration of five years [48]. Patients with intermediate-risk tumors require either one-year full-dose BCG (induction therapy followed by three weekly instillations at three, six, and twelve months) or instillations with chemotherapy (optimal regimen not known) for one year. The final decision should be based on the patient’s risk profile, as well as the efficacy and complications of each instillation therapy [49]. Patients with intermediate-risk tumors require an individualized follow-up cystoscopy and cytology scheme (in-between that for low- and high-risk tumors) [50].

Patients with high-risk tumors require intravesical full-dose BCG instillations for up to three years (induction therapy followed by three weekly instillations at three, six, twelve, 18, 24, 30, and 36 months) [51]. Early RC can also be discussed [52]. Patients with very high-risk tumors require early RC and those who are unfit or refuse immediate RC should undergo the same BCG regimen as patients with high-risk tumors [53]. Patients with high-risk tumors and patients with very high-risk tumors treated with BCG require cystoscopy with urinary cytology at three months. If negative, a subsequent cystoscopy with cytology is required every three months for two years, and, thereafter, every six months until five years of follow-up and subsequently once a year. In other words, for intermediate- and high-risk tumors, regular lifelong cystoscopy is mandatory, given that recurrences are also common in the long term. Yearly imaging of the upper tract imaging (with computed tomography urography) is also recommended in these cases [54].

4.7 Management of muscle-invasive bladder cancer

Bladder cancer is diagnosed in about 25% of the patients in a muscle-invasive stage [55]. RC with neoadjuvant chemotherapy is considered the gold standard for patients with muscle-invasive bladder cancer (without neoadjuvant chemotherapy for those with non-muscle-invasive disease) [56]. Alternatively, in patients with contraindications for surgery, and in those wanting to preserve their urinary bladder, a trimodality therapy (TUR-B, chemotherapy, and radiation therapy) should be considered [57]. It is generally reserved for patients with relatively smaller tumors, no lymphatic metastases, no extensive or multifocal CIS, no hydronephrosis related to the tumor, and good bladder function. In well-selected cases, the long-term survival rates of trimodality bladder-preserving therapy are comparable to those of RC [58].

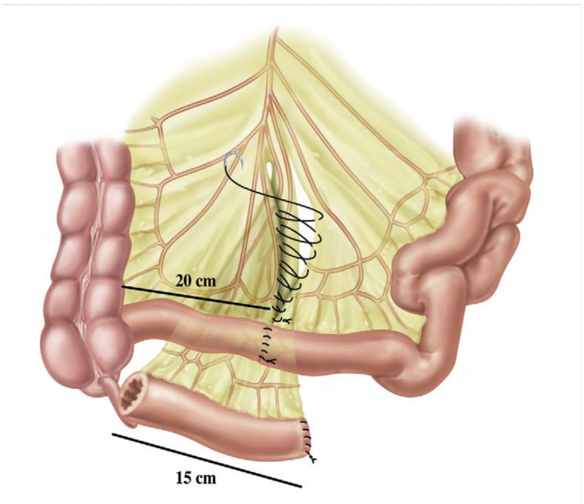
In patients with metastatic disease that are fit for platinum, cisplatin-based combination chemotherapy (in most cases gemcitabine/cisplatin) is recommended. In patients who are unfit for cisplatin, but are fit for carboplatin, carboplatin should be used in combination with gemcitabine [59]. In patients unfit for any platinum-based chemotherapy, management with a checkpoint inhibitor should be considered [60].

4.8 Radical cystectomy

Regardless of the type of histology, RC is the treatment of choice in patients with non-metastatic disease. The operation involves the removal of the urinary bladder with lymph node dissection (without in non-muscle invasive disease or multimorbid patients) and an appropriate urinary diversion [61]. Different surgical approaches have been described to remove the urinary bladder and improve the oncological and functional outcomes. Still, to date, no consensus exists in terms of which surgical approach displays better short- and long-term outcomes [62]. In recent years, minimally invasive RC has become an alternative to open RC [63]. Indeed, it seems that laparoscopic and robot-assisted RC have gained popularity by reducing intraoperative blood loss and length of hospital stay (by about one to two days), while offering similar short- and long-term oncological and functional outcomes compared to open RC [64]. Nevertheless, it should be highlighted that it remains unclear whether these favorable properties may translate into an overall benefit for the patients and the healthcare system since minimally invasive RC leads to increased intraoperative costs and longer operative time [65]. Therefore, to date, major guidelines recommend selecting experienced RC centers and not specific techniques [66].

Irrespective of the surgical technique, RC in men typically includes the concomitant removal of the prostate with the seminal vesicles and the distal part of the ureters. In women, RC typically includes the concomitant removal of the uterus, urethra, adjacent vagina, and the distal part of the ureters [67]. Standard lymph-node dissection is an integral part of RC in patients with muscle-invasive disease. It displays both a diagnostic value in terms of staging and a therapeutic value in terms of tumor excision [68]. Lymphadenectomy typically involves the removal of lymph nodes up to the common iliac bifurcation (including presacral lymph nodes, as well as lymph nodes of the obturator fossa, external and internal iliac vessels) [69].

Urinary diversion after RC is typically classified into an incontinent or a continent procedure [70]. Among incontinent procedures, ileal conduit is the most commonly preferred urinary diversion due to its well-known results and lower complication rates [71]. For the ileal conduit, an ileal segment, about 15 cm long, is isolated approximately 20 cm proximally to the ileocecal valve [72]. The ureters are spatulated and anastomosed to the proximal end of the ileal segment, while the distal end of the ileal segment is sutured to the abdominal wall through an opening (stoma) [73]. The urinary diversion with ileal conduit is presented in Figure 1.



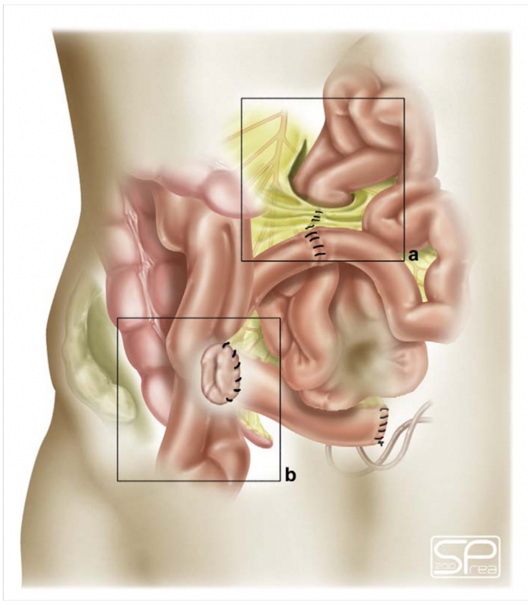


Figure 1: Urinary diversion with an ileal conduit. Reproduced after license acquirement (License Number: 5593750714631, License Date: 21/07/2023, Licensed Content Publisher: Elsevier, Licensed Content Publication: European Urology Supplements, Licensed Content Title: Ileal Conduit as the Standard for Urinary Diversion After Radical Cystectomy for Bladder Cancer, Licensed Content Author: Renzo Colombo, Richard Naspro).

In patients with multiple comorbidities, ureters can be directly implanted into the abdominal wall either through a single or separate opening. This approach is called ureterocutaneostomy and is predominantly reserved for old or multimorbid patients. Due to the direct implantation of the ureters to the skin, stenosis of the anastomosis, and ascending urinary tract infections are more often observed after ureterocutaneostomy compared to urinary diversions using the bowel to create an intestinal stoma [74]. The urinary diversion with ureterocutaneostomy is presented in Figure 2.

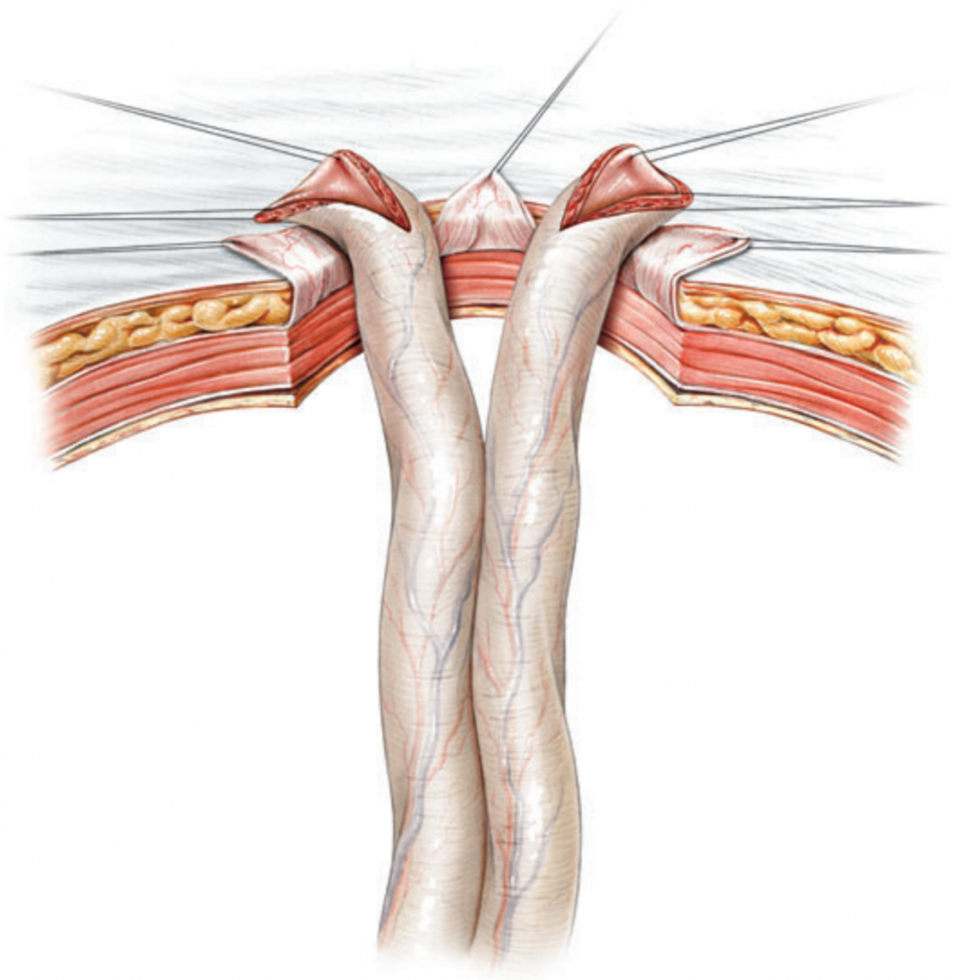


Figure 2: Urinary diversion with a ureterocutaneostomy. Reproduced after license acquirement (License Number: 5600830834103, License Date: 02/08/2023, Licensed Content Publisher: John Wiley and Sons, Licensed Content Publication: BJU International, Licensed Content Title: Cutaneous ureterostomy, Licensed Content Author: Armin Pycha, Michele Lodde, Lukas Lusuardi).

Among continent procedures, neobladder is most commonly preferred since it offers an orthotopic bladder substitution [75]. An ileal segment, about 70 cm long, is isolated approximately 20 cm proximally to the ileocecal valve. The ileal segment is then typically arranged in a W- or U-shape and its limbs are sutured to one another. The distal part is anastomosed with the urethra and the ureters are implanted into the neobladder at a convenient site. The urinary diversion with orthotopic bladder substitution is presented in Figure 3. Alternatively, cutaneous procedures such as a catheterizing pouch can also be used in well-selected cases [76]. Still, it should be underlined that approximately 25% of all patients undergoing RC are not eligible for a continent urinary diversion [77].

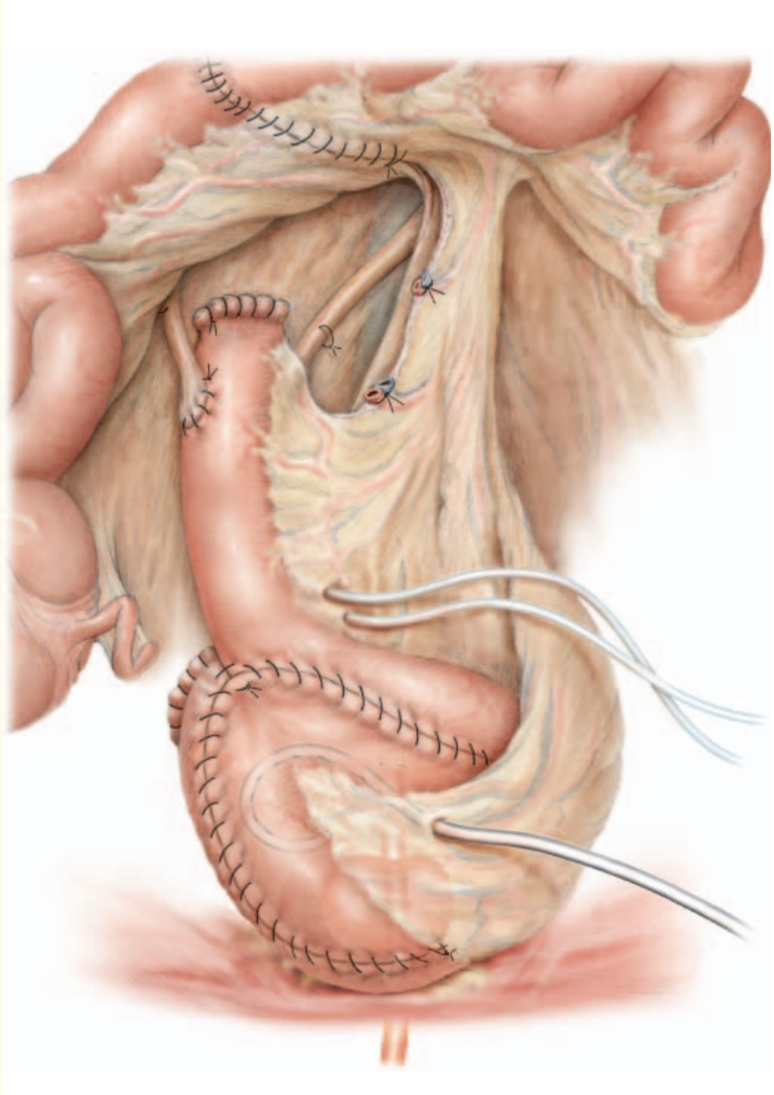


Figure 3: Urinary diversion with an orthotopic neobladder. Reproduced after license acquirement (License Number: 5600830120654, License Date: 02/08/2023, Licensed Content Publisher: John Wiley and Sons, Licensed Content Publication: BJU International, Licensed Content Title: Orthotopic ileal neobladder, Licensed Content Author: H. Danuser, C. Varol, U.E. Studer).

Among the different contraindications for a continent urinary diversion, chronic kidney disease (at least IIIb stage) is considered one of the most important since it can lead to hyperchloremic metabolic acidosis [78]. Urine storage in the bowel mucosa of a continent urinary diversion results in reabsorption of urea, potassium, and chloride, and in excretion of sodium and bicarbonate. In turn, this increased acid load cannot be processed by the kidneys of patients with chronic kidney disease, leading to electrolyte and pH problems [79]. Importantly, apart from gastrointestinal complications and other typical complications encountered also with incontinent urinary diversions, patients receiving a continent urinary diversion develop frequently lower urinary tract symptoms (incontinence, retention, infections, post-void residual urine, and other voiding problems) [80]. Indeed, major meta-analyses and clinical trials suggest that satisfaction rates and quality of life are similar between continent and incontinent urinary diversions in the long-term [81].

4.9 Perioperative outcomes after radical cystectomy

Currently, open RC remains the standard surgical procedure, even though the adoption of robot-assisted RC has been increasing during the last few years [82]. Despite the recent surgical advancements and improvements in terms of the operation technique and the management of patients, postoperative complications after RC are inevitable [83]. RC is associated with high rates of perioperative morbidity and mortality, prolonged hospital stay, and significant treatment-related costs [84]. It should be highlighted that perioperative complications occur in most patients undergoing RC [85]. Approximately 20% of them are severe or life-threatening, prolong the hospital stay and lead to 8% perioperative mortality.

Evidence deriving from high-volume, high-quality data suggests that the 30-day mortality after RC is about 3% and the 90-day mortality about 8% [86]. In the CORAL study from 2016 (one of the most important three-arm RCTs on the field) that compared open versus laparoscopic versus robotic RC and included 59 patients in total, the authors concluded that about 50% of all patients undergoing RC experience at least one complication and about 20% of all patients undergoing RC experience one severe complication in the first 30 days after surgery [87]. It seems that the commonest perioperative complications after RC comprise infections (including sepsis), bleeding (with or without transfusion), acute renal failure, ileus, thromboembolism, and other major cardiopulmonary complications [88].

A recent high-quality systematic review and meta-analysis including 44 RCTs concluded that complications following RC are quite common [89]. Overall, gastrointestinal complications affect 19%, infections 17%, cardiovascular complications 9%, genital and urologic complications 7%, and respiratory complications 7% of all patients undergoing RC. The most common complications included transfusion (36%), ileus (14%), readmission (14%), urinary tract infection (8%), lymphocele (4%), sepsis (4%), acute renal failure (4%), arrhythmia (4%), reoperation (3%) deep vein thrombosis (3%), pulmonary artery embolism (2%) and myocardial infarction (1%). Based on the Clavien-Dindo classification, 14% of all patients undergoing RC suffer from Clavien-Dindo I perioperative complications, 31% from Clavien-Dindo II, 7% from Clavien-Dindo IIIa, 5% from Clavien-Dindo IIIb, 3% from Clavien-Dindo IV, and 2% of all patients undergoing RC die (Clavien-Dindo V) [90]. Nevertheless, the authors could not assess the overall morbidity and mortality of the included patients due to unavailable patient-level data. This could have been possible with the Comprehensive Complication Index (CCI), a tool that enables the calculation of the overall morbidity of each patient based on the Clavien-Dindo classification. The CCI estimates the gravity of the overall complication burden of each patient based on a scale from 0 (no complications) to 100 (death) [91].

4.10 Caseload volume and radical cystectomy

RC is also associated with high costs and prolonged hospital stay, which may further increase when perioperative complications occur. Previous studies on the field have suggested that, in Germany, approximately 6,000 RCs are performed every year [92]. Accumulating evidence suggests that an increased annual hospital volume, and not an increased surgeon volume, is associated with better perioperative outcomes for major oncological surgeries such as esophagectomy, pancreatectomy, and RC [93]. Large retrospective cohort studies, as well as systematic reviews and meta-analyses, indicate that hospital caseload is a major determinant of perioperative morbidity and mortality after RC [94,95].

Hospitals with higher caseload volume are associated with better perioperative outcomes in terms of mortality and morbidity [96]. It seems that high-volume hospitals provide the required infrastructure, as well as experienced medical and paramedical personnel that may result in early identification and adequate treatment of postoperative complications [97]. Furthermore, experienced operative teams can lead to a reduction of the operative time, prevention of postoperative complications, and optimization of the management of intraoperative complications [98].

In the first high-quality systematic review and meta-analysis on the field by Goossens-Laan et al. with ten studies and 196,978 patients, the authors suggested, after analyzing administrative data from published studies, that high-volume centers are associated with lower mortality rates (OR: 0.55; 95%CI: 0.44 to 0.69) [95]. Still, the authors pooled low- and high-volume centers based on the threshold used in each study. Nevertheless, each study used a different threshold, and a large variation in the threshold was observed, rendering the interpretation of these findings problematic. Therefore, the authors concluded in 2011 that the available literature was limited, and only a trend for better outcomes in high-volume centers could be observed. Thereafter, multiple studies based on administrative and population data have been published from Australia, Canada, China Europe, Japan, and USA [99].

The largest study on the field was published in 2013 by Ravi et al. and included 79,859 RCs from the NIS dataset. Patients were divided into three groups based on the annual hospital caseload of the center where they received RC. Low-volume centers were defined as below the lower 20-percentile (1–3 RC/year), high-volume centers as above the upper 20-percentile (≥24 RC/year), and intermediate-volume centers as above the lower 20-percentile and below the upper 20-percentile (4–23 RC/year). After adjusting for age, Charlson Comorbidity Index, race, urinary diversion, gender, insurance status, and annual income, the authors demonstrated in the multivariable analysis that low-volume centers in the USA were associated with 26%, 39%, 17%, and 75% higher odds of intraoperative complications, postoperative complications, blood transfusion, and prolonged hospital stay, respectively, compared to high-volume centers ($p < 0.03$ for all outcomes).

Accordingly, patients undergoing RC at low-volume centers displayed a 2.2-fold higher odds of in-hospital death compared to patients undergoing RC at high-volume centers ($p < 0.001$) [100]. Still, it should be noted that the authors did not report on the number and frequency of complications. Similarly, the authors did not perform separate analyzes for each complication. Based on the previous notion, it should be stressed that the separation of hospitals into low-, intermediate- and high-volume centers was arbitrarily applied based on their distribution of hospitals into quartiles and not based on current guideline recommendations.

Available evidence suggests that hospital volume rather than surgeon volume is the main driver of perioperative outcomes after RC. Mayer et al. reported lower mortality rates in surgeons performing at least eight RC/year. However, after adjusting for patient characteristics and other risk factors, surgeon volume was not associated with lower in-hospital mortality [101]. Importantly, high-volume surgeons in high-volume centers display better perioperative outcomes compared to high-volume surgeons in low-volume centers [102]. Thus, an interdisciplinary approach is mandatory for patients undergoing RC. It seems that, not only the surgeon but also the competence of the whole surgical and anesthesiology team assessing the patients preoperatively and postoperatively, as well as the experience of the nurse and physiotherapy team play a crucial role in the prevention and management of perioperative complications [103]. Additionally, early recovery/fast tract concepts after RC that include immediate enteral feeding, early postoperative patient mobilization, avoidance of medications causing paralytic ileus, and administration of prokinetic agents seem to also reduce postoperative complications [104]. Therefore, the available literature indicates that there is currently an increasing trend toward the centralization of RC to achieve better perioperative and long-term outcomes [105].

4.11 Gaps in the literature

Given that the hospital volume seems to be the main driver of perioperative outcomes after RC, a plethora of studies has attempted to identify an annual RC hospital caseload threshold that reduces perioperative morbidity and mortality [106,107]. To date, the EAU Muscle Invasive and Metastatic Bladder Cancer Guideline Panel recommends that centers should perform at least 10 RC/year, and preferably more than 20 RC/year, or, otherwise, refer patients requiring RC to hospitals that reach these annual numbers [99]. Still, this recommendation is based on a low level of evidence, considering that it derives from a systematic review that included 39 studies, which recruited a relatively low number of participants and reported conflicting data. More specifically, the EAU Muscle Invasive and Metastatic Bladder Cancer Guideline Panel performed a second systematic review on the same topic in 2019 (after this by Goossens-Laan et al. in 2011) to provide solid recommendations on the matter. Nevertheless, this was not possible since each of the included studies in this systematic review used a different threshold to define the optimal hospital volume for RC. Interestingly, this threshold ranged from 8 to 55 RC/year.

To date, all available systematic reviews have pooled studies with different thresholds in terms of defining low-, intermediate- and high-volume centers. Based on the previous notion, a meta-analysis on the topic could not be performed by the EAU Muscle Invasive and Metastatic Bladder Cancer Guideline Panel [95,99,108]. Accordingly, administrative and retrospective studies on the matter included a relatively small number of participants, classified hospitals arbitrarily into caseload categories, did not adjust outcomes for important risk factors, or did not assess in-depth the major perioperative outcomes [109–111]. That said, it seems that, despite these publications, the optimal annual caseload volume for RC remains unknown [112].

4.12 Purpose of the present study

Within this framework, this dissertation aimed to assess the German Nationwide Inpatient Data of the DRG dataset (the largest study in the field) in an attempt to evaluate both the recommended threshold proposed by the EAU and to objectively define an annual hospital volume threshold that optimizes perioperative outcomes in patients undergoing RC through sophisticated statistical analyses. This dissertation also aimed to assess in-depth the number and the frequency of complications, the mortality rates, the time-to-inpatient death, the costs of RC in Germany, and the length of hospital stay. Additionally, it evaluated the evolution of RC throughout the years as well as the distribution of hospitals in Germany into low-, moderate- and high-volume centers.

5. Material and Methods

5.1 German Nationwide Inpatient Data

All inpatient data from 2005 to 2020 were retrieved from the Federal Bureau of Statistics (Wiesbaden, Hessen, Germany) and were made available for analysis upon an agreement (LMU - 4710-2022) for the purposes of the present dissertation. The GRAND dataset contains all reimbursed inpatient cases in Germany apart from psychiatric, forensic, and military cases. All data are available and stored anonymized at the Federal Bureau of Statistics. After the implementation in 2004 of a diagnosis- and procedure-related remuneration system in Germany (the German Diagnosis Related Groups - G-DRG system), all hospitals are required to code and transfer to the Institute for the Hospital Remuneration System patient data on inpatient diagnoses, coexisting conditions, as well as on perioperative outcomes, and surgical procedures [113]. These data are mandatory for all German hospitals to receive their corresponding remuneration. These diagnoses and perioperative outcomes are coded according to the ICD-10-GM, whereas surgical procedures are coded according to the German OPS. In order to ensure uniform documentation throughout Germany, coding guidelines are provided by the German Institute for Medical Documentation and Information [114].

5.2 Eligibility criteria and coding

For the purposes of the present dissertation, all patients undergoing RC in Germany from 2005 to 2020 were identified through the OPS code 5-57. Only patients undergoing RC due to urinary bladder cancer were included (ICD code: C67 and D41.4). On the contrary, those patients that underwent concomitant nephroureterectomy (OPS code: 5-563 and 5-554) were excluded. To obtain information for further procedures, coexisting conditions, and complications, the available diagnostic and procedural codes (ICD-10-GM and OPS codes) were used [115]. The procedures, coexisting conditions, and complications based on the corresponding ICD-10-GM and OPS codes are depicted in Table 2.

Diagnosis	ICD-10-GM or OPS Code
Diabetes mellitus type 2	E10, E11, E13
Myocardial infarction	I21, I22, I24
Congestive heart failure	I099, I110, I130, I132, I255, I42 (0, 5 to 9), I43, I50
Chronic obstructive pulmonary disease	I278, I279, J4, J6 (0 to 7), J684, J701, J703
Chronic renal failure	I120, I131, I132, N03, N05, N18, N19
Thromboembolism	I26, I74, I80
Acute renal failure	N17, N99, O904
Acute respiratory failure	J960, J969, J80
Cerebrovascular accident	G45, G46, H340, I6
Dementia	F0 (0 to 3), F051, G30, G311
Pneumonia	J1 (2 to 8), J85
Hypertension	I10, I11, I12, I13
Obesity	Z68 (3 to 4), E66, E65
Sepsis	A41
Surgical wound infection	8-19 (1 to 3)
Transfusion	8-80
Ileus	K56
VAC placement	8-190
Ureterocutaneostomy	5-5642, 5-5643, 5-5647
Ileal conduit	5-565
Neobladder	5-5660, 5-5661, 5-5662, 5-5723, 5-566b, 5-5663, 5-566c, 5-577 (0 to 2)
Colostomy placement	5-455
Robotic radical cystectomy	5-987
Laparoscopic radical cystectomy	5-57601, 5-57621, 5-57611, 5-57631, 5-57641, 5-57651, 5-57661, 5-57671, 5-57681, 5-576x1

Table 2: Procedures, coexisting conditions, and complications assessed in the present study based on the corresponding ICD-10-GM and OPS codes.

5.3 Annual hospital caseload threshold

The primary outcome of the present dissertation was to evaluate multiple thresholds in an attempt to define the optimal annual hospital volume for RC that improves inpatient outcomes. Secondary outcomes included the effect of these thresholds on I) major perioperative complications, II) Treatment-related costs, and III) Length of hospital stay.

For this purpose, Youden's index (also called Youden's J statistic) based on ROC curve analyses was used [116]. The Youden's index is defined as sensitivity + specificity -1 and can take values from -1 to 1 [117]. The Youden's index is used to summarize the performance of a diagnostic test and is calculated for all points of a ROC curve [118]. The maximum value of Youden's index can be used as a criterion for identifying the optimal threshold of a diagnostic test [119].

In the present analysis, Youden's index was computed for each point of every ROC curve on perioperative outcomes. Its maximum value was selected as a criterion to identify the optimal threshold for annual hospital RC caseload in terms of mortality, important complications (sepsis, transfusion, ileus), length of hospital stay, and hospital revenues. For each diagnostic test (annual hospital caseload threshold that optimizes each outcome), the specificity, sensitivity, as well as the positive and negative predictive values were calculated.

Based on the present analyses, the optimal threshold for annual hospital RC caseload that reduces perioperative mortality was estimated at 54 RC/year, displaying a sensitivity of 58%, a specificity of 48%, a positive predictive value of 50%, and a negative predictive value of 96%. The optimal threshold for annual hospital RC caseload regarding ileus was 50 RC/year with a sensitivity of 99%, a specificity of 21%, a positive predictive value of 10%, and a negative predictive value of 91%. For sepsis, the optimal threshold for annual hospital RC caseload was 44 RC/year and displayed a sensitivity of 35%, a specificity of 68%, a positive predictive value of 62%, and a negative predictive value of 95%. Similarly, for transfusion, the optimal threshold for annual hospital RC caseload was also 44

RC/year and displayed a sensitivity of 34%, a specificity of 70%, a positive predictive value of 55%, and a negative predictive value of 49%. Moreover, the optimal threshold for annual hospital RC caseload for reducing the length of hospital stay and the inpatient costs was 71 and 76 RC/year, respectively. The findings of the ROC curve analyses are depicted in Table 3.

Complication	Hospital caseload threshold	Sensitivity	Specificity	PPV	NPV
Mortality	54	58%	48%	50%	96%
Sepsis	44	35%	68%	62%	95%
Transfusion	44	34%	70%	55%	49%
Ileus	50	99%	21%	10%	91%
Hospital stay	71	58%	79%	86%	46%
Costs	76	50%	71%	50%	66%

Table 3: Annual hospital radical cystectomy caseload threshold for major perioperative outcomes, based on the maximum Youden's index from the ROC curve analyses. NPV: negative predictive value, PPV: positive predictive value.

Thus, the optimal threshold that may improve inpatient outcomes in patients undergoing RC was set arbitrarily at 50 cases/year. Subsequently, this threshold was compared with other thresholds in terms of in-hospital morbidity, mortality, length of hospital stay, and treatment-related costs. In particular, both the thresholds proposed by the EAU (<10, 10 to 19, ≥20 RC/year) and the threshold of 70 RC/year proposed by the present analyses regarding the length of hospital stay and inpatient costs were used.

5.4 Data synthesis and statistical analysis

All hospitals in Germany that perform RCs were identified through their postal code. Subsequently, they were further subclassified based on their annual caseload to low-volume hospitals (<20 RC/year), intermediate-volume hospitals fulfilling the EAU recommendation (20-49 RC/year), and high-volume hospitals fulfilling the optimal annual threshold suggested by the present findings (≥50 RC/year). Similarly, based on the current EAU recommendations, another sub-classification was also tested defining low-volume hospitals as those hospitals that performed < 10 cases/year, intermediate-volume hospitals as those hospitals that performed 10-19 cases/year, and high-volume hospitals as those hospitals that performed ≥20 cases/year. Finally, the subclassification of <20 RC/year, 20-70 RC/year, and ≥70 RC/year was also tested.

The corresponding comparisons among low-, intermediate- and high-volume centers were undertaken using the chi-squared (categorical variables) and the ANOVA test (continuous variables). For all analyses, two-sided p-values lower than 0.05 were considered statistically significant. All continuous variables were provided as mean ± SD and all categorical variables as frequencies (proportions). A multivariable logistic and linear regression analysis was also undertaken to evaluate the different thresholds on inpatient mortality and morbidity (sepsis, transfusion, and ileus), as well as on the length of hospital stay and hospital revenues. Based on clinical relevance, all models were a priori adjusted for age, sex, obesity, hypertension, diabetes mellitus type 2, heart failure, myocardial infarction, cerebrovascular accidents, history of chronic obstructive pulmonary disease, chronic renal failure, as well as perioperative acute renal failure, pneumonia, acute respiratory failure, and placement of VAC. ORs with 95% CIs were estimated for all logistic models. The Kaplan–Meier curves with the log-rank test were also used to evaluate the role of the annual hospital RC caseload on inpatient time-to-death [120].

The DRG dataset, also known as the GRAND dataset, contains the perioperative outcomes of more than 100,000,000 inpatient cases in Germany. Due to the large volume of data that had to be processed for the present analysis, a big memory computer with a large amount of RAM was mandatory. Therefore, the final analyses were performed in a big memory computer stored in the Research Data Center of the Federal Bureau of Statistics. In order to develop the R codes that were used for the present analysis, the DRG dataset was filtered from the Research Data Center of the Federal Bureau of Statistics and sample files with 1%

of all patients undergoing RC were provided to our research team. These sample files could be processed on any computer. Subsequently, the R codes for all analyses were developed by our research team and were provided to the Research Data Center of the Federal Bureau of Statistics, which, in turn, used them unchanged to generate the final results on our behalf with the big memory computer (source: Research Data Center of the Federal Bureau of Statistics, DRG Statistics 2005-2020 own calculations). Finally, the final results, in form of tables and figures, were returned to our research team, after control of anonymity and data integrity for final evaluation and further analysis. The whole process of the data for the present dissertation is outlined in Figure 4.

For the purposes of this dissertation, sophisticated R codes were developed. Our research team provided the R codes to the Research Data Center of the Federal Bureau of Statistics, which used them unchanged and performed all analyses with a big memory computer. All analyses were undertaken with the RStudio, update 2022.07.2.

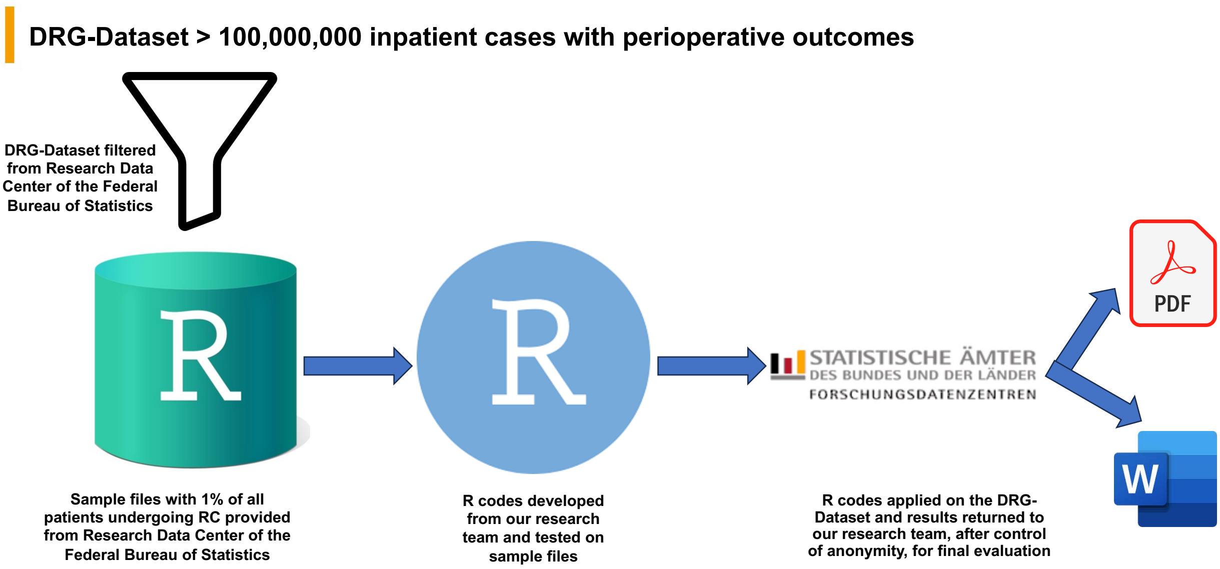


Figure 4: Filtering, sampling, code development, and processing of the DRG dataset.

6. Results

6.1 Baseline characteristics

Overall, a total of 95,841 patients were included in the present dissertation. Their mean age was 69 ± 9.8 years. Accordingly, the mean length of hospital stay was 24 ± 14 days, and the in-hospital costs were 17,580 ± 13,110 Euros per patient. A total of 76,190 (79%) patients were men, 8,433 (8.8%) were obese, whereas 53,281 (56%) had hypertension and 18,285 (19%) diabetes. The majority of all patients received urinary diversion with ileal conduit (52,430 patients, 55%), whereas the neobladder reconstruction was preferred in 29,700 (31%) cases. Interestingly, only 4,134 (4,3%) patients were operated with a minimally invasive technique (robot-assisted or laparoscopic). Overall, 1,667 (1.7%) patients received a colostomy intraoperatively. Acute kidney disease was reported perioperatively in 10,496 (11%) cases, acute respiratory failure in 10,771 (11%) cases, pneumonia in 5,273 (5.5%) cases, ileus in 9,622 (10%) cases, and sepsis in 5,429 (5.7%) cases. 50,238 (52%) patients required in-hospital transfusion and 4,691 (4.9%) VAC placement. Based on the optimal threshold proposed by the EAU and by the present analyses (<20, 20 to 49, and ≥50 RC/year), a total of 28,291 (30%) patients received RC in a low-, 49,616 (52%) in an intermediate- and 17,934 (19%) in a high-volume hospital. The baseline characteristics of all patients and the comparisons among low-, intermediate-, and high-volume centers are depicted in Table 4.

Characteristic	**Overall**, n = 95,841	**<20**, n = 28,291	**20-49**, n = 49,616	**≥50**, n = 17,934	**p-value**
Males	76,190 (79%)	22,233 (79%)	39,508 (80%)	14,449 (81%)	**<0.001**
Age (years)	69 ± 9.8	69 ± 9.6	69 ± 9.8	69 ± 10.2	**<0.001**
Obesity	8,433 (8.8%)	2,578 (9.1%)	4,464 (9%)	1,391 (7.8%)	**<0.001**
Hypertension	53,281 (56%)	16,056 (57%)	27,583 (56%)	9,642 (54%)	**<0.001**
Diabetes	18,285 (19%)	5,594 (20%)	9,452 (19%)	3,239 (18%)	**<0.001**
Dementia	1,306 (1.4%)	417 (1.5%)	702 (1.4%)	187 (1%)	**<0.001**
Chronic kidney disease	14,863 (16%)	4,796 (17%)	7,963 (16%)	2,104 (12%)	**<0.001**
Chronic heart failure	7,749 (8.1%)	2,574 (9.1%)	4,097 (8.3%)	1,078 (6%)	**<0.001**
Chronic cerebrovascular disease	3,182 (3.3%)	934 (3.3%)	1,750 (3.5%)	498 (2.8%)	**<0.001**
History of myocardial infarction	1,242 (1.3%)	365 (1.3%)	669 (1.3%)	208 (1.2%)	0.16
History of thromboembolism	4,131 (4.3%)	1,153 (4.1%)	2,023 (4.1%)	955 (5.3%)	**<0.001**
Chronic obstructive pulmonary disease	11,186 (12%)	3,389 (12%)	5,939 (12%)	1,858 (10%)	**<0.001**
Hospital stay (days)	24 ± 14	26 ± 15	24 ± 15	22 ± 13	**<0.001**
Perioperative costs (Euros)	17,580 ± 13,110	17,778 ± 13,350	17,593 ± 13,527	17,279 ± 11,580	**0.003**

Characteristic	**Overall**, n = 95,841	**<20**, n = 28,291	**20-49**, n = 49,616	**≥50**, n = 17,934	**p-value**
Operative technique					**<0.001**
Open	91,707 (95%)	27,624 (98%)	46,926 (94%)	17,157 (95%)	
Laparoscopic	1,506 (2%)	402 (1%)	963 (2%)	141 (2%)	
Robotic	2,628 (3%)	265 (1%)	1,727 (4%)	636 (4%)	
Ureterocutaneostomy	10,568 (11%)	3,524 (12%)	5,655 (11%)	1,389 (7.7%)	**<0.001**
Ileal conduit	52,430 (55%)	14,975 (53%)	27,630 (56%)	9,825 (55%)	**<0.001**
Neobladder reconstruction	29,700 (31%)	8,574 (30%)	14,823 (30%)	6,303 (35%)	**<0.001**
Colostomy	1,667 (1.7%)	478 (1.7%)	902 (1.8%)	287 (1.6%)	0.12
Acute respiratory failure	10,771 (11%)	3,638 (13%)	5,677 (11%)	1,456 (8.1%)	**<0.001**
Acute kidney disease	10,496 (11%)	3,094 (11%)	5,543 (11%)	1,859 (10%)	**0.012**
Inpatient transfusion	50,238 (52%)	15,636 (55%)	25,263 (51%)	9,339 (52%)	**<0.001**
Inpatient pneumonia	5,273 (5.5%)	1,665 (5.9%)	2,708 (5.5%)	900 (5.0%)	**<0.001**
Inpatient VAC placement	4,691 (4.9%)	1,489 (5.3%)	2,484 (5.0%)	718 (4.0%)	**<0.001**
Inpatient sepsis	5,429 (5.7%)	1,760 (6.2%)	2,744 (5.5%)	925 (5.2%)	**<0.001**
Inpatient ileus	9,622 (10%)	2,997 (11%)	5,020 (10%)	1,605 (8.9%)	**<0.001**

Table 4: Baseline characteristics of the included patients based on the recommended annual hospital caseload for radical cystectomy (<20, 20 to 49, and ≥50 cases/year). Variables are presented as mean ± standard deviation or frequencies (proportions). The one-way ANOVA test was performed for comparisons among continuous variables and the chi-squared test for categorical variables. The bold cells indicate statistically significant p-values.

6.2 Baseline characteristics and annual hospital caseload

In centers performing less than 20 RC/year, patients were statistically significantly older and presented more often with hypertension, diabetes mellitus type 2, chronic heart failure, and chronic kidney disease compared to centers performing 20 to 49 RC/year or more than 50 RC/year. The latter can be explained by the fact that minimally invasive RC ($p < 0.001$) and more sophisticated urinary diversions (such as neobladder) ($p < 0.001$) were more often performed in high-volume centers. Still, it should be stressed that the absolute differences between the three groups were minimal and do not reflect a clinical difference. Patients who underwent RC in high-volume hospitals developed fewer postoperative complications. In particular, complications such as acute kidney disease ($p = 0.012$), acute respiratory failure ($p < 0.001$), pneumonia ($p < 0.001$), and VAC placement ($p < 0.001$) were less commonly encountered in high-volume centers (Table 4). Of note, both the mortality rates and the annual number of RC performed in Germany did not significantly change throughout the years and were not affected by the COVID-19 pandemic and its lockdown period. The annual trends of RC are presented in Figure 5.

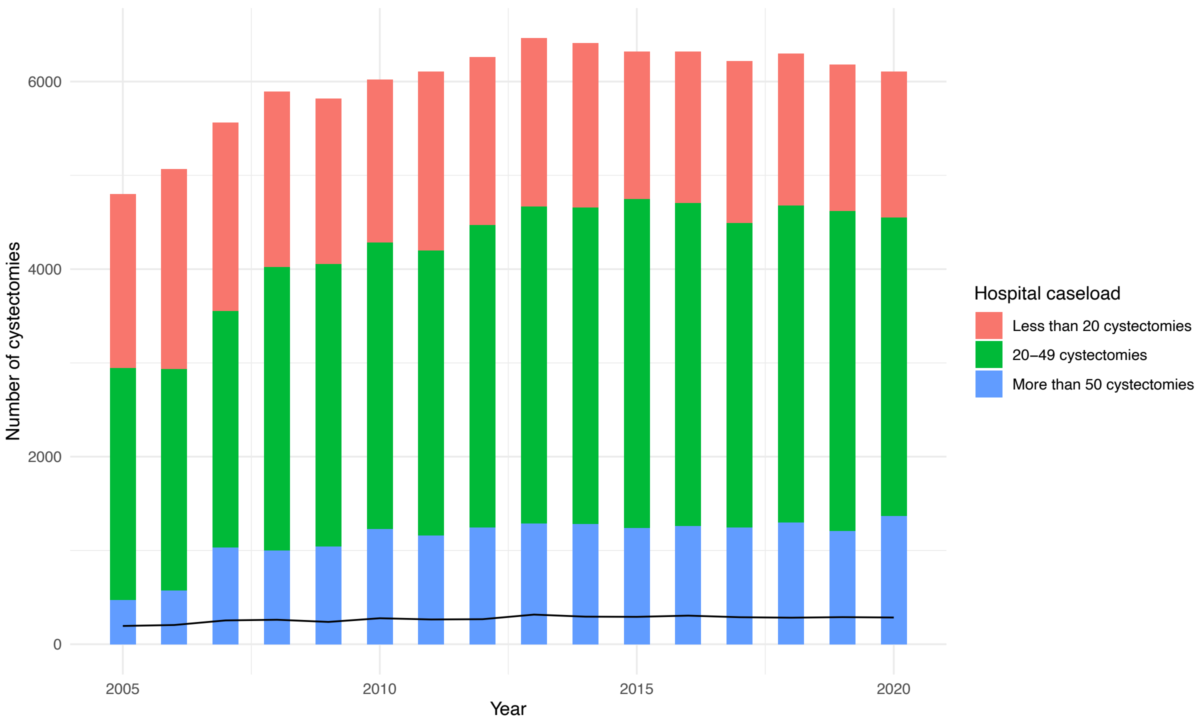


Figure 5: The annual trends for radical cystectomy based on hospital caseload (<20, 20 to 49, and ≥50 cases/year). The line represents the annual inpatient mortality for all patients.

6.3 **Perioperative outcomes based on caseload volume of <20, 20-49 and ≥50 RC/year**

A total of 4,313 (4.5%) in-hospital deaths occurred after RC. Among them, 1,477 (5.2%) patients died in low-, 2,216 (4.5%) in intermediate- and 620 (3.5%) in high-volume hospitals ($p < 0.001$). In the multivariable analysis after adjusting for major determinants, intermediate and high-volume hospitals were associated with lower in-hospital mortality rates compared to low-volume hospitals (OR: 0.84, 95% CI: 0.78 to 0.91, $p < 0.001$ and OR: 0.72, 95% CI: 0.64 to 0.8, $p < 0.001$, respectively). This was also observed in the time-to-death analysis (log-rank test: $p < 0.001$).

It should be noted that perioperative complications such as ileus, sepsis, and transfusion occurred more often in patients undergoing RC in low-volume centers ($p < 0.001$). In the multivariable analysis after adjusting for major determinants, intermediate- and high-volume hospitals were associated with lower rates in-hospital sepsis rates compared to low-volume centers (OR: 0.89, 95% CI: 0.84 to 0.96, $p < 0.001$ and OR: 0.91, 95% CI: 0.83 to 0.99, $p = 0.036$, respectively). Based on the same analyses, comparing low- to intermediate- and high-volume centers, the in-hospital transfusion rates were only statistically significant for intermediate-volume hospitals ($p < 0.001$), while the in-hospital ileus rates were only statistically significant for high-volume hospitals ($p < 0.001$).

Accordingly, low-volume hospitals were associated with longer length of hospital stay and higher inpatient costs ($p < 0.001$). In the multivariable analysis after adjusting for major determinants, the length of hospital stay was shorter by 2.7 (95% CI: 2.4 to 2.9, $p < 0.001$) days and the in-hospital costs were lower by 457 (95% CI: 207 to 707, $p < 0.001$) Euros in patients receiving RC in high-volume hospitals compared to low-volume hospitals. Of note, patients undergoing RC in intermediate-volume hospitals displayed only significantly shorter length of hospital stay by 1.1 (95% CI: 0.9 to 1.3, $p<0.001$) days compared to low-volume hospitals. All multivariable analyses are available in Table 5.

Annual cystec-tomy caseload	Mortality		Sepsis		Transfusion		Ileus		Length of hospi-tal stay		Costs	
	OR	p-value	OR	p-value	OR	p-value	OR	p-value	Beta	p-value	Beta	p-value
< 20	—	—	—	—	—	—	—	—	—	—	—	—
20-49	0.84 (0.78, 0.91)	**<0.001**	0.89 (0.84, 0.96)	**<0.001**	0.84 (0.82, 0.87)	**<0.001**	0.96 (0.91, 1.01)	0.088	-1.1 (-1.3, -0.92)	**<0.001**	184 (-16, 383)	0.071
≥ 50	0.72 (0.64, 0.8)	**<0.001**	0.91 (0.83, 0.99)	**0.036**	0.97 (0.93, 1.01)	0.09	0.87 (0.81, 0.93)	**<0.001**	-2.7 (-2.9, -2.4)	**<0.001**	457 (207, 707)	**<0.001**

Table 5: Multivariable logistic and linear regression analysis for the effect of annual hospital cystectomy caseload on perioperative mortality, sepsis, transfusion, ileus, length of hospital stay, and costs based on the recommended from the EAU annual hospital caseload and on the optimal annual hospital caseload proposed by the present analyses (<20, 20 to 49 and ≥50 cases/year). All models are adjusted for sex, age, obesity, history of chronic obstructive pulmonary disease, heart failure, chronic renal failure, cerebrovascular accident, hypertension, diabetes, as well as perioperative acute renal failure, acute respiratory failure, pneumonia, myocardial infarction, surgical wound infection, and VAC placement. The bold cells indicate statistically significant p-values. OR: odds ratio.

6.4 Perioperative outcomes based on caseload volume of <50 and ≥50 RC/year

Most hospitals in Germany perform less than 50 RC per year (Figure 6).

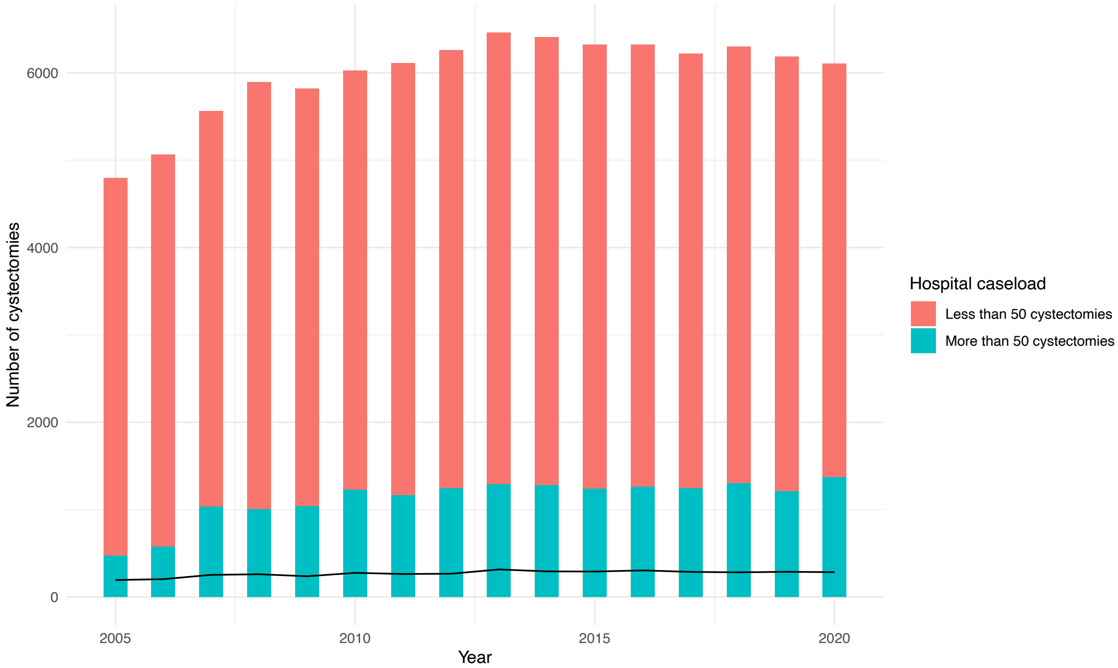


Figure 6: The annual trends for radical cystectomy based on hospital caseload (<50 and ≥50 cases/year). The line represents the annual inpatient mortality for all patients.

In the multivariable logistic and linear regression analysis comparing centers performing more than 50 cases/year versus fewer than 50 cases/year and after adjusting for major determinants, the optimal annual RC hospital caseload proposed by the present analyses (≥50 RC/year) was associated with lower mortality rates ($p < 0.001$) and ileus ($p < 0.001$), as well as with shorter length of hospital stay ($p < 0.001$) and in-hospital costs ($p = 0.002$). Based on the latter, patients receiving RC in high-volume hospitals presented a 20% decrease in mortality, and an 11% decrease in ileus complications, and also stayed 2 days shorter in the hospital. All analyses are available in Table 6.

Annual cystec- tomy case- load	Mortality		Sepsis		Transfusion		Ileus		Length of hospi- tal stay		Costs	
	OR	p-value	OR	p-value	OR	p-value	OR	p-value	Beta	p-value	Beta	p-value
< 50	—	—	—	—	—	—	—	—	—	—	—	—
≥ 50	0.8 (0.72, 0.88)	**<0.001**	0.98 (0.9, 1.06)	0.5	1.08 (1.04 , 1.12)	**<0.001**	0.89 (0.84 , 0.95)	**<0.001**	-2 (- 2.2, - 1.8)	**<0.001**	335 (124, 546)	**0.002**

Table 6: Multivariable logistic and linear regression analysis for the effect of annual hospital cystectomy caseload on perioperative mortality, sepsis, transfusion, ileus, length of hospital stay, and costs based on the optimal annual hospital caseload proposed by the present analyses (<50 and ≥50 cases/year). All models are adjusted for sex, age, obesity, history of chronic obstructive pulmonary disease, heart failure, chronic renal failure, cerebrovascular accident, hypertension, diabetes, as well as perioperative acute renal failure, acute respiratory failure, pneumonia, myocardial infarction, surgical wound infection, and VAC placement. The bold cells indicate statistically significant p-values. OR: odds ratio.

6.5 Perioperative outcomes based on caseload volume of <10, 10 to 19 and ≥20 RC/year

Based on this subclassification deriving from the recommendations by the EAU, 6,312 (6.6%) patients were operated in low- (<10 RC/year), 21,979 (23%) in intermediate- (10 to 19 RC/year), and 67,550 (70.4%) in high-volume (≥20 RC/year) centers. Patients who were operated in low-volume centers displayed fewer preoperative comorbidities even though the absolute differences between the three groups were minimal and may not reflect a clinical difference. In particular, the patient's age ($p = 0.003$) and the proportion of patients with hypertension ($p < 0.001$), diabetes ($p = 0.001$), chronic kidney disease ($p < 0.001$), and chronic heart failure ($p < 0.001$) were lower in low-volume centers. Nevertheless, their hospital stay was longer ($p < 0.001$) and was associated with more perioperative costs ($p = 0.037$) compared to high-volume centers. On the contrary, minimally invasive techniques ($p < 0.001$) and more complex urinary diversions such as neobladder ($p < 0.001$) were more common in high-volume centers. Furthermore, patients who were operated in high-volume centers displayed, in most cases, fewer postoperative complications. More specifically, the proportion of patients with acute respiratory failure ($p < 0.001$), pneumonia ($p = 0.003$), and VAC placement ($p = 0.002$) were lower in high-volume centers (Table 7). A total of 338 (5.4%) deaths occurred in low-, 1,139 (5.2%) in intermediate- and 2,836 (4.2%) in high-volume centers ($p < 0.001$) (Figure 7).

Characteristic	**<10**, n = 6,312	**10-19**, n = 21,979	**≥20**, n = 67,550	**p-value**
Males	4,952 (78%)	17,281 (79%)	53,957 (80%)	**<0.001**
Age (years)	70 ± 9.4	69 ± 9.7	69 ± 9.9	**0.003**
Obesity	595 (9.4%)	1,983 (9%)	5,855 (8.7%)	0.052
Hypertension	3,643 (58%)	12,413 (56%)	37,225 (55%)	**<0.001**
Diabetes	1,267 (20%)	4,327 (20%)	12,691 (19%)	**0.001**
Dementia	105 (1.7%)	312 (1.4%)	889 (1.3%)	0.053

Characteristic	**<10**, n = 6,312	**10-19**, n = 21,979	**≥20**, n = 67,550	**p-value**
Chronic kidney disease	1,185 (19%)	3,611 (16%)	10,067 (15%)	**<0.001**
Chronic heart failure	618 (9.8%)	1,956 (8.9%)	5,175 (7.7%)	**<0.001**
Chronic cerebrovascular disease	208 (3.3%)	726 (3.3%)	2,248 (3.3%)	0.98
History of myocardial infarction	79 (1.3%)	286 (1.3%)	877 (1.3%)	0.95
History of thromboembolism	107 (1.7%)	447 (2.0%)	1,453 (2.2%)	**0.042**
Chronic obstructive pulmonary disease	754 (12%)	2,635 (12%)	7,797 (12%)	0.16
Hospital stay (days)	26 ± 15	26 ± 15	24 ± 14	**<0.001**
Perioperative costs (Euros)	17,626 ± 12,708	17,822 ± 13,530	17,506 ± 13,019	**0.037**
Operative technique				**<0.001**
Laparoscopic	75 (1.2%)	327 (1.5%)	1,104 (1.6%)	
Open	6,196 (98%)	21,428 (97%)	64,083 (95%)	
Robotic	41 (0.6%)	224 (1%)	2,363 (3.5%)	
Ureterocutaneostomy	841 (13%)	2,683 (12%)	7,044 (10%)	**<0.001**
Ileal conduit	3,366 (53%)	11,609 (53%)	37,455 (55%)	**<0.001**
Neobladder reconstruction	1,763 (28%)	6,811 (31%)	21,126 (31%)	**<0.001**
Colostomy	106 (1.7%)	372 (1.7%)	1,189 (1.8%)	0.75

Characteristic	**<10**, n = 6,312	**10-19**, n = 21,979	**≥20**, n = 67,550	**p-value**
Acute respiratory failure	796 (13%)	2,842 (13%)	7,133 (11%)	**<0.001**
Acute kidney disease	729 (12%)	2,365 (11%)	7,402 (11%)	0.21
Inpatient transfusion	3,634 (58%)	12,002 (55%)	34,602 (51%)	**<0.001**
Inpatient pneumonia	379 (6%)	1,286 (5.9%)	3,608 (5.3%)	**0.003**
Inpatient VAC placement	324 (5.1%)	1,165 (5.3%)	3,202 (4.7%)	**0.002**
Inpatient sepsis	378 (6%)	1,382 (6.3%)	3,669 (5.4%)	**<0.001**
Inpatient ileus	754 (12%)	2,243 (10%)	6,625 (9.8%)	**<0.001**

Table 7: Baseline characteristics of the included patients based on the recommended by the EAU annual hospital caseload for radical cystectomy (<10, 10 to 19, and ≥20 RC/year). Variables are presented as mean ± standard deviation or frequencies with proportions. The one-way ANOVA test was performed for comparisons among continuous variables and the chi-squared test for categorical variables. The bold cells indicate statistically significant p-values.

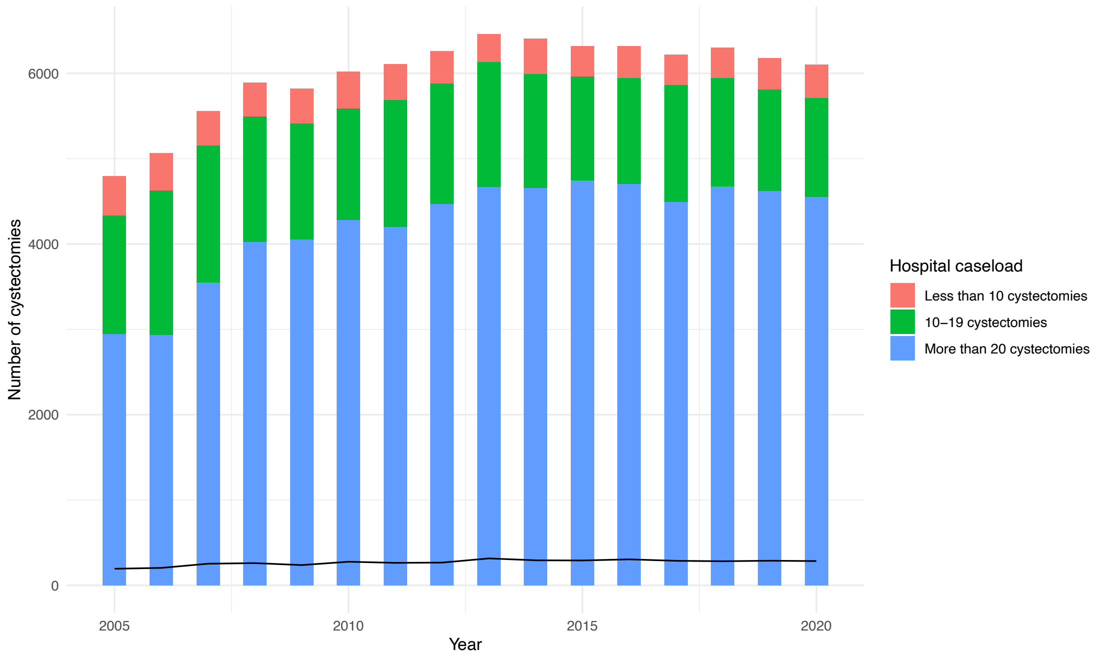


Figure 7: The annual trends for radical cystectomy based on hospital caseload (<10, 10 to 19, and ≥20 RC/year). The line represents the annual in-hospital mortality for all patients.

In the multivariable analysis after adjusting for major determinants, high-volume centers were associated with a lower inpatient mortality rate compared to low-volume centers (OR: 0.8, 95% CI: 0.71 to 0.92, p < 0.001). The latter was also observed in the time-to-death analysis (log-rank test: p = 0.034, Figure 8).

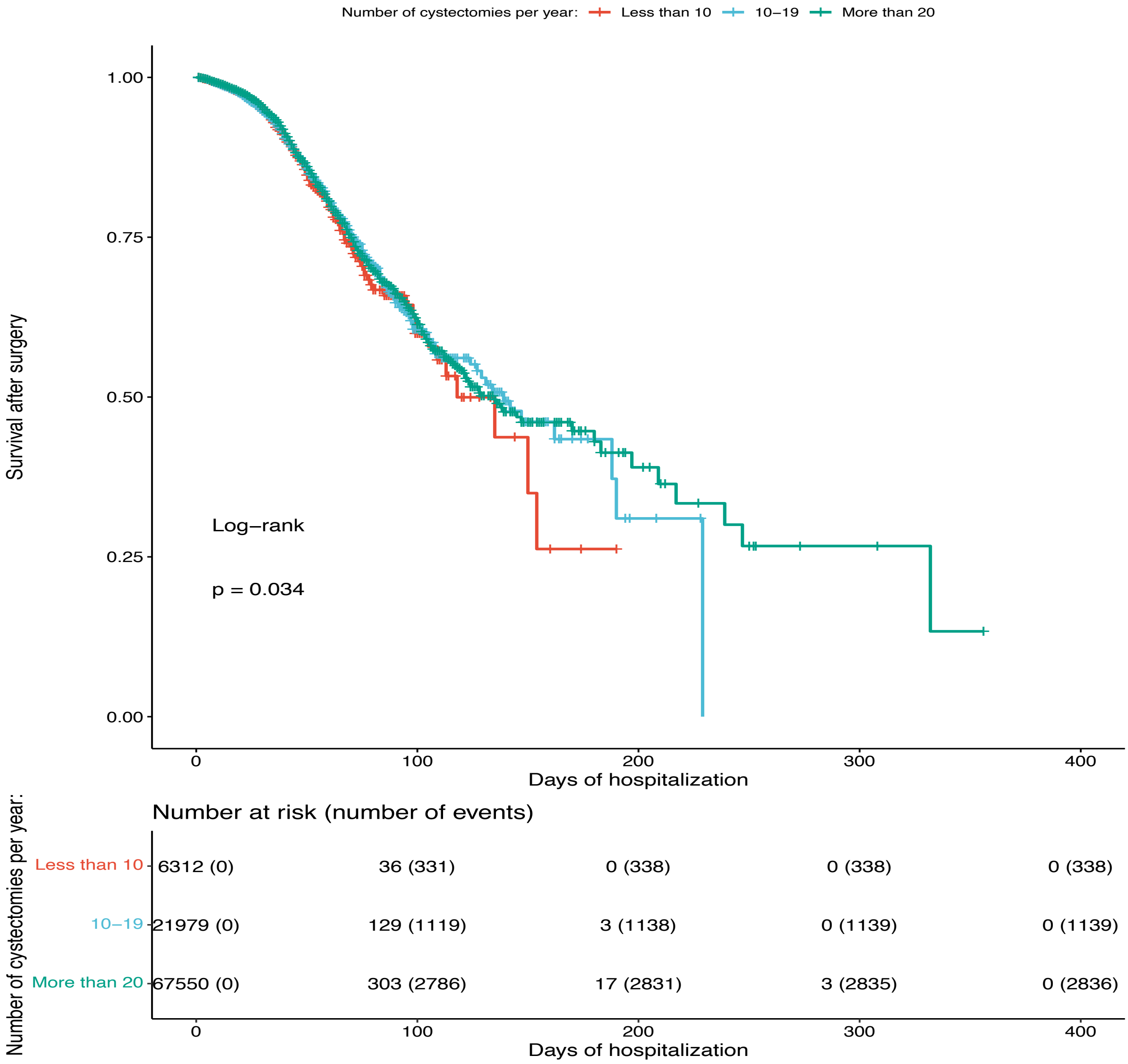


Figure 8: Kaplan-Maier curve for inpatient mortality based on the recommended by the EAU annual hospital caseload for radical cystectomy (<10, 10 to 19, and ≥20 RC/year).

Based on this subclassification proposed by the EAU, sepsis, ileus, and transfusion were less common in high-volume centers ($p < 0.001$). In the multivariable analysis after adjusting for major determinants, intermediate- and high-volume centers were associated with lower rates of transfusion (OR: 0.9, 95% CI: 0.85 to 0.95, $p < 0.001$ and OR: 0.81, 95% CI: 0.76 to 0.85, $p < 0.001$, respectively) and ileus (OR: 0.83, 95% CI: 0.76 to 0.91, $p < 0.001$ and OR: 0.81, 95% CI: 0.75 to 0.88, $p < 0.001$, respectively) compared to low-volume centers. Nevertheless, the rates of sepsis were similar among low-, intermediate ($p = 0.2$), and high-volume centers ($p = 0.4$).

Patients undergoing RC in high-volume centers presented shorter length of hospital stay and lower perioperative costs compared to low-volume centers. After adjusting for major baseline and perioperative risk factors, the length of hospital stay was shorter by 1.6 (95% CI: 1.3 to 1.9, $p < 0.001$) days and the perioperative costs were lower by 369 (95% CI: 13 to 725, $p = 0.042$) Euros in patients undergoing RC in high-volume centers compared to low-volume centers. All multivariable analyses are available in Table 8.

Annual cystec-tomy case-load	Mortality		Sepsis		Transfusion		Ileus		Length of hospital stay		Costs	
	OR	**p-value**	**OR**	**p-value**	**OR**	**p-value**	**OR**	**p-value**	**Beta**	**p-value**	**Beta**	**p-value**
< 10	—	—	—	—	—	—	—	—	—	—	—	—
10-19	0.99 (0.86, 1.14)	0.9	1.08 (0.95, 1.23)	0.2	0.9 (0.85, 0.95)	**<0.001**	0.83 (0.76, 0.91)	**<0.001**	-0.08 (-0.43, 0.26)	0.6	143 (-245, 531)	0.5
≥ 20	0.80 (0.71, 0.92)	**<0.001**	0.95 (0.85, 1.07)	0.4	0.81 (0.76, 0.85)	**<0.001**	0.81 (0.75, 0.88)	**<0.001**	-1.6 (-1.9, -1.3)	**<0.001**	369 (13, 725)	**0.042**

Table 8: Multivariable logistic and linear regression analysis for the effect of annual hospital cystectomy caseload (<10, 10 to 19, and ≥20 RC/year) on perioperative mortality, sepsis, transfusion, ileus, length of hospital stay, and costs. All models are adjusted for sex, age, obesity, history of chronic obstructive pulmonary disease, heart failure, chronic renal failure, cerebrovascular accident, hypertension, diabetes, as well as perioperative acute renal failure, acute respiratory failure, pneumonia, myocardial infarction, surgical wound infection, and VAC placement. The bold cells indicate statistically significant p-values. OR: odds ratio.

6.6 Perioperative outcomes based on caseload volume of <20, 20 to 69 and ≥70 RC/year

Based on this subclassification, 28,291 (29.5%) patients were operated in low- (< 20 RC/year), 60,695 (63.3%) in intermediate- (20 to 69 RC/year), and 6,855 (7.2%) in high-volume (≥ 70 RC/year) centers. As demonstrated in the previous analyses, patients undergoing RC in centers performing less than 20 cases/year were older and presented with more preoperative comorbidities compared to centers performing 20 to 69 cases/year and more than 70 cases/year. The latter can be explained because minimally invasive RC ($p < 0.001$) and more sophisticated urinary diversions (such as neobladder) ($p < 0.001$) were more often performed in intermediate- and high-volume centers. Still, it should be stressed that the absolute differences between the three groups were minimal and do not reflect a clinical difference. Patients who underwent RC in high-volume hospitals developed fewer postoperative complications. In particular, all evaluated complications: acute kidney disease ($p = 0.009$), acute respiratory failure ($p < 0.001$), pneumonia ($p = 0.001$), and VAC placement ($p < 0.001$) were less commonly encountered in high-volume centers (Table 9). A total of 1,477 (5.2%) deaths occurred in low-, 2,644 (4.4%) in intermediate- and 192 (2.8%) in high-volume centers ($p < 0.001$) (Figure 9).

Characteristic	**<20**, n = 28,291	**20-69**, n = 60,695	**≥70**, n = 6,855	**p-value**
Males	22,233 (79%)	48,379 (80%)	5,578 (81%)	
Age (years)	69.2 ± 9.6	69.3 ± 9.9	68.3 ± 10.2	**<0.001**
Obesity	2,578 (9.1%)	5,360 (8.8%)	495 (7.2%)	**<0.001**
Hypertension	16,056 (57%)	33,554 (55%)	3,671 (54%)	**<0.001**
Diabetes	5,594 (20%)	11,511 (19%)	1,180 (17%)	**<0.001**
Dementia	417 (1.5%)	835 (1.4%)	54 (0.8%)	**<0.001**
Chronic kidney disease	4,796 (17%)	9,377 (15%)	690 (10%)	**<0.001**

Characteristic	**<20**, n = 28,291	**20-69**, n = 60,695	**≥70**, n = 6,855	**p-value**
Chronic heart failure	2,574 (9.1%)	4,803 (7.9%)	372 (5.4%)	**<0.001**
Chronic cerebrovascular disease	934 (3.3%)	2,085 (3.4%)	163 (2.4%)	**<0.001**
History of myocardial infarction	365 (1.3%)	800 (1.3%)	77 (1.1%)	0.40
History of thromboembolism	1,153 (4.1%)	2,552 (4.2%)	426 (6.2%)	**<0.001**
Chronic obstructive pulmonary disease	3,389 (12%)	7,131 (12%)	666 (9.7%)	**<0.001**
Hospital stay (days)	25.5 ± 15.0	23.9 ± 14.3	21.5 ± 11.6	**<0.001**
Perioperative costs (Euros)	17,778.1 ± 13,350.0	17,540.0 ± 13,363.6	17,227.2 ± 9,751.4	**0.013**
Operative technique				**<0.001**
Laparoscopic	402 (1.4%)	1,078 (1.8%)	26 (0.4%)	
Open	27,624 (98%)	57,378 (95%)	6,705 (98%)	
Robotic	265 (0.9%)	2,239 (3.7%)	124 (1.8%)	
Ureterocutaneostomy	3,524 (12%)	6,696 (11%)	348 (5.1%)	**<0.001**
Ileal conduit	14,975 (53%)	33,723 (56%)	3,732 (54%)	**<0.001**
Neobladder reconstruction	8,574 (30%)	18,434 (30%)	2,692 (39%)	**<0.001**
Colostomy	478 (1.7%)	1,085 (1.8%)	104 (1.5%)	0.20
Acute respiratory failure	3,638 (13%)	6,650 (11%)	483 (7.0%)	**<0.001**

Characteristic	**<20**, n = 28,291	**20-69**, n = 60,695	**≥70**, n = 6,855	**p-value**
Acute kidney disease	3,094 (11%)	6,726 (11%)	676 (9.9%)	**0.009**
Inpatient transfusion	15,636 (55%)	31,292 (52%)	3,310 (48%)	**<0.001**
Inpatient pneumonia	1,665 (5.9%)	3,266 (5.4%)	342 (5.0%)	**0.001**
Inpatient VAC placement	1,489 (5.3%)	2,938 (4.8%)	264 (3.9%)	**<0.001**
Inpatient sepsis	1,760 (6.2%)	3,384 (5.6%)	285 (4.2%)	**<0.001**
Inpatient ileus	2,997 (11%)	6,069 (10.0%)	556 (8.1%)	**<0.001**

Table 9: Baseline characteristics of the included patients based on the recommended by the EAU annual hospital caseload for radical cystectomy (<20, 20 to 69, and ≥70 RC/year). Variables are presented as mean ± standard deviation or frequencies with proportions. The one-way ANOVA test was performed for comparisons among continuous variables and the chi-squared test for categorical variables. The bold cells indicate statistically significant p-values.

Figure 9: The annual trends for radical cystectomy based on hospital caseload (<20, 20 to 69, and ≥70 RC/year). The line represents the annual in-hospital mortality for all patients.

In the multivariable analysis after adjusting for major determinants, intermediate and high-volume hospitals were associated with lower in-hospital mortality rates compared to low-volume hospitals (OR: 0.83, 95% CI: 0.77 to 0.9, $p < 0.001$ and OR: 0.59, 95% CI: 0.5 to 0.69, $p < 0.001$, respectively). The latter was also observed in the time-to-death analysis (log-rank test: $p < 0.001$, Figure 10).

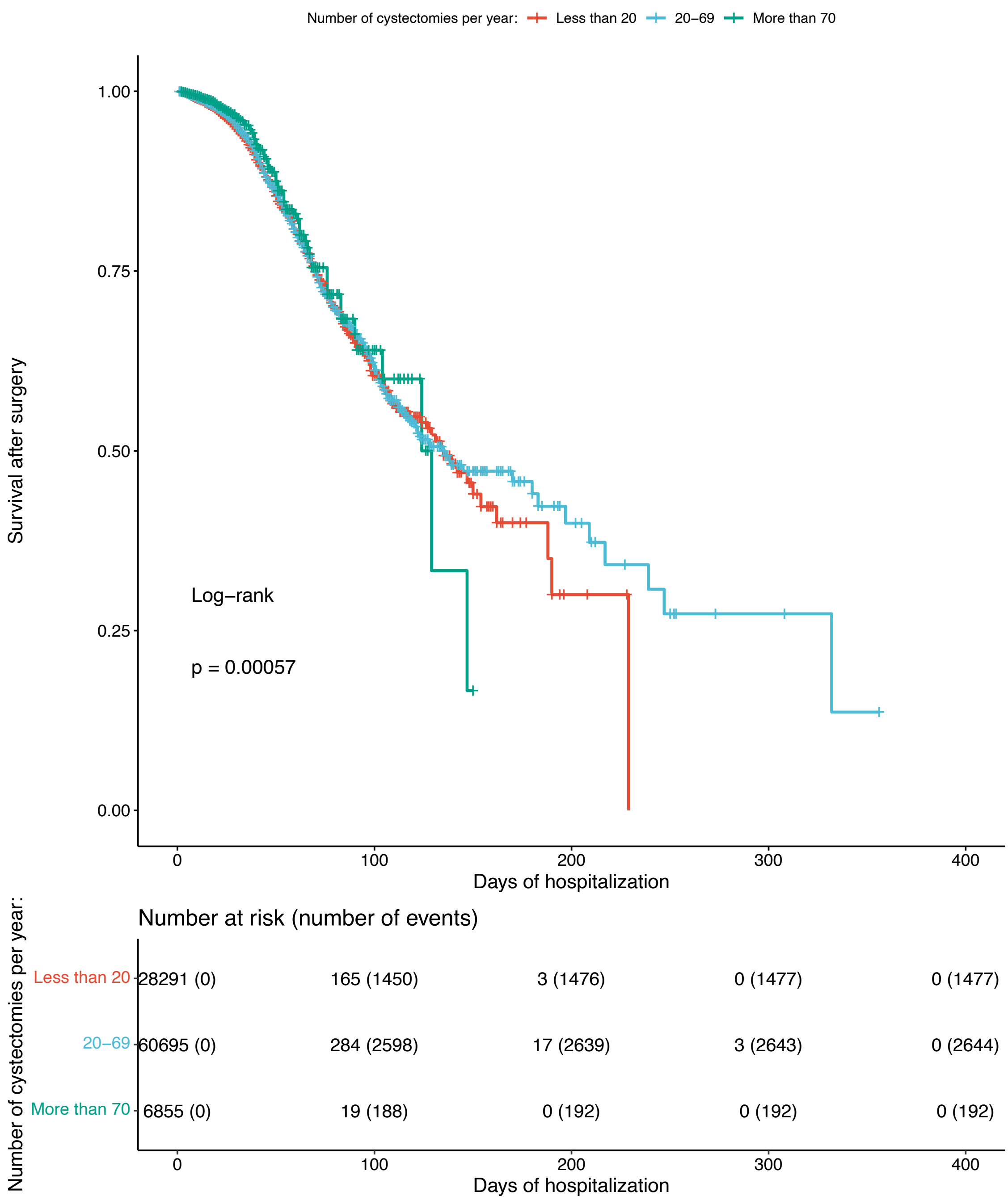


Figure 10: Kaplan-Maier curve for inpatient mortality based on the recommended by the EAU annual hospital caseload for radical cystectomy (<20, 20 to 69, and ≥70 RC/year).

Based on this subclassification, sepsis, ileus, and transfusion were less common in intermediate- and high-volume centers ($p < 0.001$). In the multivariable analysis after adjusting for major determinants, intermediate- and high-volume centers were associated with lower rates of transfusion (OR: 0.88, 95% CI: 0.85 to 0.9, $p < 0.001$ and OR: 0.85, 95% CI: 0.8 to 0.9, $p < 0.001$, respectively), ileus (OR: 0.95, 95% CI: 0.91 to 1, $p = 0.04$ and OR: 0.79, 95% CI: 0.71 to 0.87, $p < 0.001$, respectively) and sepsis (OR: 0.92, 95% CI: 0.86 to 0.98, $p = 0.007$ and OR: 0.73, 95% CI: 0.63 to 0.83, $p < 0.001$, respectively) compared to low-volume centers.

Patients undergoing RC in intermediate- and high-volume centers presented shorter length of hospital stay and lower perioperative costs. After adjusting for major determinants, the length of hospital stay in intermediate- and high-volume centers was shorter by 1.3 (95% CI: 1.2 to 1.5, $p < 0.001$) and by 3.2 (95% CI: 2.9 to 3.5, $p < 0.001$) days compared to low-volume centers. Accordingly, the perioperative costs were lower by 220 (95% CI: 27 to 413, $p = 0.026$) and by 576 (95% CI: 234 to 918, $p < 0.001$) Euros in patients undergoing RC in intermediate- and high-volume centers compared to low-volume centers. All multivariable analyses are available in Table 10.

Annual cystectomy caseload	Mortality		Sepsis		Transfusion		Ileus		Length of hospital stay		Costs	
	OR	p-value	OR	p-value	OR	p-value	OR	p-value	Beta	p-value	Beta	p-value
< 20	—	—	—	—	—	—	—	—	—	—	—	—
20-69	0.83 (0.77, 0.9)	**<0.001**	0.92 (0.86, 0.98)	**0.007**	0.88 (0.85, 0.9)	**<0.001**	0.95 (0.91, 1)	**0.04**	-1.3 (-1.5, -1.2)	**<0.001**	220 (27, 413)	**0.026**
≥ 70	0.59 (0.5, 0.69)	**<0.001**	0.73 (0.63, 0.83)	**<0.001**	0.85 (0.8, 0.9)	**<0.001**	0.79 (0.71, 0.87)	**<0.001**	-3.2 (-3.5, -2.9)	**<0.001**	576 (234, 918)	**<0.001**

Table 10: Multivariable logistic and linear regression analysis for the effect of annual hospital cystectomy caseload (<20, 20 to 69, and ≥70 RC/year) on perioperative mortality, sepsis, transfusion, ileus, length of hospital stay, and costs. All models are adjusted for sex, age, obesity, history of chronic obstructive pulmonary disease, heart failure, chronic renal failure, cerebrovascular accident, hypertension, diabetes, as well as perioperative acute renal failure, acute respiratory failure, pneumonia, myocardial infarction, surgical wound infection, and VAC placement. The bold cells indicate statistically significant p-values. OR: odds ratio

7. Discussion

7.1 Results Interpretation

The present dissertation, which is based on high-volume, real-world data, indicates that the cutoff of 50 RC/year should be considered a major determinant for perioperative mortality and morbidity. Similarly, this cutoff seems to shorten the length of hospital stay and reduce treatment-related costs. Taking into consideration that multiple analyses with large-scale and high-quality data were performed, this dissertation suggests that setting the RC caseload cutoff to 50 cases/year (and not to 20 cases/year as proposed by the EAU) could improve important inpatient outcomes. Importantly, increasing the RC caseload cutoff above 50 cases/year to 70 cases/year was still associated with a statistically significant improvement in important perioperative outcomes. Nevertheless, it should be noted that it might be extremely difficult for most centers worldwide to achieve more than 70 RC/year [121].

7.2 Mortality after radical cystectomy

It should be highlighted that the nationwide data from Germany between 2005 and 2020, indicate that most centers performing RC achieve the minimum requirement of 20 cases/year. Nevertheless, only 19% of all patients were operated in centers performing more than 50 RC/year and only 7.2% in centers performing more than 70 RC/year. After adjusting for major determinants in terms of complications, RC in hospitals performing more than 50 cases/year was significantly associated with a 28% reduction in mortality compared to centers performing fewer than 20 cases/year, while RC in centers with 20-49 cases/year was associated with a 16% reduction in mortality compared to centers performing fewer than 20 cases/year. Similarly, RC in hospitals performing more than 70 cases/year was significantly associated with a 41% reduction in mortality compared to centers performing fewer than 20 cases/year, while RC in centers with 20-69 cases/year was associated with a 17% reduction in mortality compared to centers performing fewer than 20 cases/year. The latter showcases that a further increase in annual hospital caseload might further improve mortality. Moreover, no statistically significant differences in terms of mortality were detected between centers performing less than 10 RC/year and 10-19 RC/year. Importantly, the time-to-death analysis showed better outcomes in patients undergoing RC in high-volume centers.

Based on the present real-world data from Germany, a total of 4.5% in-hospital deaths occurred after RC from 2005 to 2020 and a 4.4% 100-day mortality was observed. This proportion is higher than the 2% mortality rate estimated by Katsimperis et al. in a recent meta-analysis pooling data from 44 RCTs with 4,919 patients [89]. Still, it should be noted that, in most of the included RCTs, RCs were performed in high-volume or excellence centers by high-volume surgeons. Similarly, it seems that in high-volume centers, minimally-invasive RC displays a ≤ 3% mortality for all types of urinary diversion [122]. On the contrary, population-based cohort studies and administrative data from the USA suggest that the perioperative mortality after RC is about 2% at 30 days and 3.4% to 8% at 90 days, which is comparable to the mortality rates reported in this study [123]. Accordingly, data from the Netherlands suggest a 30-day mortality of 1.9% and a 90-day mortality of 6% [124]. Recent data from England show an improvement in perioperative outcomes and a decrease in perioperative mortality over the last year. In particular, the 30-day mortality decreased from 5.2% to 2.1% from 1998 to 2010, whereas the 90-day mortality decreased from 10.3% to 5.1% [125].

7.3 Morbidity after radical cystectomy

Patients undergoing RC in centers that performed fewer than 20 RC/year developed more inpatient complications. In particular, after adjusting for major determinants, RC in hospitals performing more than 50 cases/year was significantly associated with a 9% reduction in sepsis rates and a 13% reduction in ileus rates compared to centers performing fewer than 20 cases/year, while RC in centers with 20-49 cases/year was associated with an 11% reduction in sepsis rates and a 16% reduction in transfusions compared to centers performing fewer than 20 cases/year. Similarly, RC in hospitals performing more than 70 cases/year was significantly associated with a 27% reduction in sepsis rates, a 15% reduction in transfusions, and a 21% reduction in ileus rates compared to centers performing fewer than 20 cases/year, while RC in centers with 20-69 cases/year was associated with an 8% reduction in sepsis rates, a 12% reduction in transfusions and a 5% reduction in ileus rates compared to centers performing fewer than 20 cases/year. These findings showcase that a further increase in annual hospital caseload might further improve not only mortality but also morbidity. Moreover, RC in hospitals performing 10 to 19 cases/year was significantly associated with a 10% reduction in transfusions and an 18% reduction in ileus rates compared to centers performing fewer than 10 cases/year. Nevertheless, centers performing at least 20 RC/year displayed better perioperative outcomes in terms of mortality and morbidity, indicating that hospitals that perform less than 10 RC/year should try to refer patients to other centers and that a minimum of 20 RC per year and hospital should be implemented. Importantly, perioperative mortality and morbidity seem to be lower in Germany compared to other countries with similar healthcare systems [126].

Based on the present real-world data from Germany, a total of 10% cases of postoperative of ileus occurred. Paralytic ileus is a mild postoperative complication that can be avoided by enteral feeding, patient mobilization, avoidance of opiates, and use of prokinetic agents. It is typically managed conservatively with nasogastric intubation and parenteral nutrition [127]. On the contrary, obstructive ileus needs surgical exploration. The incidence of postoperative paralytic ileus ranges from 2% to 24%, with potential patient risk factors including increased age and BMI. Interestingly, gum chewing, omission of a nasogastric tube, and avoidance of bowel preparation reduce the incidence of paralytic ileus [128]. Data from the RAVOR RCT with 350 participants indicate that minimally invasive and open RC seem to display similar rates of postoperative ileus (22% versus 20%, respectively) [129].

In Germany, 52% of all patients undergoing RC required perioperative transfusion. Cohort studies suggest that approximately 16% to 73% of all patients undergoing RC may need allogenic perioperative blood transfusion [130]. Population-based studies from Canada suggest that, although transfusion rates are decreasing during the last few years, still, about 60% of all patients undergoing RC require perioperative blood transfusion [131]. High-quality data published from the Department of Urology of the LMU Hospital demonstrate that intraoperative blood transfusion during RC was necessary in 36% of cases, while postoperative blood transfusion in 18% [132]. It also seems that blood transfusion increases overall and cancer-specific mortality, as well as cancer recurrence [133]. The latter might be attributed to the immunosuppressive effect of perioperative blood transfusion. It seems that surgical manipulations during RC may cause hematogenic tumor cell circulation, which in the case of perioperative immunosuppression through blood transfusion might facilitate the seeding of circulating tumor cells [134].

In Germany, 5.7% of all patients undergoing RC developed sepsis. Sepsis is a life-threatening complication requiring intensive care management and broad-spectrum antibiotic administration. Postoperative sepsis increases mortality, prolongs the length of hospital stay, and is associated with additional perioperative costs [135]. Nationwide data from England suggest that the rate of 90-day sepsis after RC is about 10% and that it has further increased during the last years [136]. Furthermore, data from the USA suggest that sepsis occurs in about 8% of all patients and its occurrence is independent of age [137]. Importantly, a higher risk of urinary tract infections and septicemia are reported among patients who receive a continent urinary diversion compared to those who receive ileal conduit [138].

In the present study, 11% of all patients undergoing RC developed acute kidney disease. Acute kidney disease is associated with significant perioperative morbidity and mortality and may lead to severe chronic kidney disease in the long-term [139]. The perioperative incidence of acute kidney disease after RC ranges from 4 to 35% [140,141]. Overall, 4.9% of all patients required perioperative VAC placement either as a preventive or as a therapeutic measure. It seems that negative pressure wound therapy decreases surgical infections and aids in faster recovery after RC [142]. Moreover, 11% of all patients developed acute respiratory failure and 5.5% pneumonia. The latter is in line with studies assessing the prevalence of complications after RC, which suggest that respiratory complications occur in 7% of all patients undergoing RC [143,144].

7.4 Length of hospital stay and hospital revenues after radical cystectomy

After undergoing RC, patients in Germany remain in the hospital for about 24 days and their perioperative costs exceed 15000 Euros. Both length of hospital stay and hospital revenues seem to improve when patients are operated in high-volume centers. More specifically, after adjusting for major determinants, RC in hospitals performing more than 50 cases/year was associated with a statistically significant reduction of 2.7 days in the length of hospital stay and a reduction of 457 euros in costs compared to centers performing fewer than 20 cases/year, while RC in centers with 20-49 cases/year was associated only with a statistically significant reduction of 1.1 days in the length of hospital stay compared to centers performing fewer than 20 cases/year. Similarly, RC in hospitals performing more than 70 cases/year was associated with a statistically significant reduction of 3.2 days in the length of hospital stay and a reduction of 576 euros in costs compared to centers performing fewer than 20 cases/year, while RC in centers with 20-69 cases/year was associated with a statistically significant reduction of 1.3 days in the length of hospital stay and a reduction of 220 euros in costs compared to centers performing fewer than 20 cases/year. Moreover, no statistically significant differences in terms of length of hospital stay and costs were detected between centers performing less than 10 RC/year and 10-19 RC/year.

The mean length of hospital stay in Germany for RC was 24 days, but it seems to be affected by the outliers who stayed multiple days in hospital. Nevertheless, the mean hospital stay is, indeed, longer than that in the USA which is about 10 days [145]. In England, the median length of hospital stay is about 11 days, whereas in the Netherlands 14 days [146,147]. Importantly, minimally-invasive RC seems to reduce the length of hospital stay by about one to two days [148]. Prolonged hospital stay is associated with further complications, subsequent utilization of healthcare resources, and increased costs of care [149]. Risk factors that prolong hospital stay after RC are patient comorbidities, advanced tumor stage, prior neoadjuvant chemotherapy, and RC at lower-volume hospitals [150].

The mean hospital revenues in Germany for RC are 17,580 Euros. This sum is comparable to other countries worldwide. Minimally invasive RC seems to cost about 1,000 to 2,000 Euros more compared to open RC [151]. Moreover, the overall costs of RC with ileal conduit are about 1,000 less than RC with orthotopic urinary diversion [152]. In a multi-institutional, multinational study across Europe, the mean cost of robot-assisted RC was estimated to be 14,773 Euros [153]. The cost of RC in the USA varies between 13,000 and 31,000 Euros in different studies in the literature and is higher in patients undergoing minimally-invasive RC [154–156]. In England, the cost of open RC is about 12,500 Euros, whereas the cost of robot-assisted RC is about 15,000 Euros [157]. The costs of RC in other countries such as China and the Netherlands are similar to those in Germany [158,159]. It seems that the most effective way to decrease perioperative costs after RC is to decrease the number and the severity of postoperative complications, to reduce the operating time, and to increase the number of cases performed by each hospital [160].

7.5 Available evidence for hospital caseload

The present dissertation supports the adoption of a minimum RC hospital caseload threshold. Even though the Guideline Panel of the EAU on Muscle-invasive Bladder Cancer proposed a threshold of 20 RC/year, the present findings propose increasing this threshold to 50 RC/year to achieve optimal perioperative outcomes. Based on these results, the threshold of 20 RC/year proposed by the EAU, should be reconsidered since it was not based on hospital- or patient-level analyses. More specifically, although the Guideline Panel of the EAU on Muscle-invasive Bladder Cancer undertook a high-quality systematic review with a rigorous methodology, the low level of existing evidence, as well as the heterogeneity of the included studies in terms of selection criteria and applied thresholds for hospital caseload did not permit the authors to perform a meta-analysis and directly calculate a solid hospital caseload threshold from the available studies. Based on the previous notion, the Guideline Panel suggested, based mainly on expert opinions, that centers performing RC should undertake at least 10, and preferably more than 20 RC/year. This dissertation demonstrates that hospitals should undertake at least 20, and preferably more than 50 RC/year. Furthermore, centers that manage to perform more than 70 RC/year should be considered excellence centers. The aforementioned thresholds not only lead to a substantial improvement in inpatient morbidity and mortality but also reduce the length of hospital stay and inpatient costs. Interestingly, the German guidelines on bladder cancer suggest that, since the annual hospital and surgeon caseload for RC has only been defined from retrospective studies, no clear recommendations can be made about the minimum required number of annual RC per surgeon or per hospital that can improve perioperative outcomes [161].

A plethora of available studies in the literature have already attempted to determine an optimal hospital threshold for RC. In a high-volume retrospective analysis with 6,790 patients, Arora et al. concluded that major inpatient complications reach a plateau at 45–50 RC/year after assessing the United States National Inpatient Sample . Moreover, Richters et al. demonstrated a statistically significant decrease in terms of postoperative mortality in hospitals performing more than 30 RC/year compared to hospitals performing fewer than 30 RC/year after assessing the Netherlands Cancer Registry with 9,287 patients [163].

Nevertheless, apart from these high-quality studies, most existing studies have arbitrarily applied a hospital caseload based on the distribution of hospitals performing RC in percentiles from each database [164]. Therefore, estimations of RC hospital caseload threshold display important variety. In previous studies, hospitals that perform at least two RC/year have been considered low-volume centers, while hospitals that perform more than 50 RC/year have been considered high-volume centers [165]. To complicate things further, healthcare policymakers in countries such as the United Kingdom or the Netherlands obligate hospitals to perform a minimum of 20 RC/year or at least 50 RC and radical prostatectomies per year [166]. In an attempt to harmonize perioperative outcomes and heterogeneity in the literature, multiple patient-level analyses with different thresholds were performed. These analyses suggest that centers that perform fewer than 20

RC/year should try to refer patients with bladder cancer, while centers that reach at least 50 RC/year should be considered referral centers. Moreover, centers that exceed 70 RC/year should be considered excellence centers.

It should be noted that the present dissertation, not only provides evidence that a threshold of 50 RC per year might be more accurate compared to the proposed by the EAU threshold of 20 RC per year but also corroborates and strengthens the findings of available studies on perioperative outcomes after RC [167]. Based on nationwide data, patients undergoing RC in Germany are relatively old with multiple comorbidities such as chronic kidney disease, chronic obstructive pulmonary disease, and heart failure [132,168]. Given that smoking, previous radiotherapy, and metabolic disorders are considered among the main risk factors for muscle-invasive bladder cancer, most patients at diagnosis display multiple comorbidities which negatively affect perioperative mortality and morbidity [169].

7.6 **Operative techniques and radical cystectomy**

In Germany, it seems that continent urinary diversions are widely performed. About one-third of all patients undergoing RC received a neobladder. This proportion was even higher among patients undergoing surgery in high-volume centers. On the contrary, simpler urinary diversions such as ureterocutaneostomy were more common in low-volume centers. In an analysis of the British Association of Urological Surgeons cystectomy audit and Hospital Episodes Statistics data, ileal conduit was the commonest urinary diversion after RC with 86% cases, followed by orthotopic neobladder with 5.3% cases. A continent cutaneous pouch was preferred in 1.9% of all patients, a rectal diversion in 0.2% of all patients, while 6.3% of all patients received another urinary diversion (in most cases ureterocutaneostomy), or no data were available.

Analyses from the NIS dataset show that ileal conduit is preferred in about 87% of the cases, while ureterocutaneostomy is rarely applied in the USA (1.1%) [92]. Administrative data from the Netherlands present comparable trends to Germany for the type of urinary diversion, since about 62% of all patients operated in the Netherlands receive ileal conduit, 7% receive continent cutaneous reservoir and

10% receive an orthotopic neobladder [138]. Of note, it seems that the type of urinary diversion (continent versus incontinent) does not vary significantly based on the selected surgical approach (open versus minimally invasive) [170].

It seems that, in Germany, robot-assisted RC is not yet widely implemented even in high-volume centers. The overall proportion of laparoscopic RC was estimated at 2% and the proportion of robotic RC was estimated at 3%. On the contrary, in the USA, laparoscopic RC is performed only in 0.9% of all cases but robotic RC is performed in 20.5% of all cases [121]. Similar proportions have been reported from experienced centers in Italy. Overall, it seems that 70% of all patients undergo open RC, 25% robotic RC, and 3.4% laparoscopic RC [171]. Nevertheless, a trend for a swift of RC to a robotic approach is observed in most countries [172].

7.7 COVID and radical cystectomy

Interestingly, inpatient mortality remained stable from 2005 to 2020 and the COVID-19 pandemic with its lockdown period did not seem to impact both inpatient mortality and the annual number of RCs performed in Germany [173,174]. This may be explained by the fact that, after the COVID-19 pandemic outbreak, the Guidelines Office of the EAU published recommendations on the management of urological conditions. The treatment of muscle-invasive bladder cancer was prioritized despite the major disruption of routine hospital services [175,176]. Indeed, oncological surgeries displayed low cancellation rates during the initial pandemic waves. In particular, the cancellation rates in Europe for different oncological surgeries were: 27% for TUR-B, 21% for RC, 21% for nephroureterectomy, 18% for radical nephrectomy, and 8% for radical orchiectomy. Interestingly, radical prostatectomy presented an increased cancellation rate of 43% [177]. Still, it should be highlighted that despite the treatment backlog in urological surgery during the COVID-19 pandemic, all oncological surgeries were soon rescheduled, and the healthcare system recovered relatively promptly after the lockdown period [178].

7.8 Strengths and limitations

RC is a necessary procedure for the management of aggressive bladder cancer with high complication rates [82]. In this context, this dissertation provides the first analysis to address perioperative outcomes in a holistic approach, using multiple sophisticated statistical methods. The GRAND study is considered one of the largest and most precise administrative and population-based datasets worldwide. Its findings were also evaluated by the Research Data Center of the Federal Bureau of Statistics for data integrity [179]. Although this study does not provide a high level of evidence due to its retrospective design, it may raise clinical awareness about the importance of centralization for bladder cancer management. Furthermore, the analyses of the GRAND study were not pre-specified. Thus, the findings of the present dissertation can only be considered hypothesis-generating. In an attempt to overcome these problems, the Youden's index was used to determine the optimal thresholds not only for mortality and important inpatient complications but also for the length of hospital stay and costs.

Even though this study contains the largest analysis assessing the annual RC hospital caseload on inpatient mortality, morbidity, length of hospital stay, and hospital revenues, it should be recognized that its findings are not devoid of some limitations that need to be considered. Firstly, the analyses are based on retrospective, administrative data, and, thus, are prone to coding errors, misclassification, or inconsistencies. Based on the previous notion, the morbidity analyses were restricted only to ileus, sepsis, and transfusion. Even though the billing data of the German nationwide inpatient database present a high degree of accuracy and are regularly checked by independent physician task forces from health insurances, important information is missing. For example, data such as the oncological status of the patients based on their histology, TNM classification, and surgical margins, as well as their laboratory findings are not available.

Moreover, data on the annual surgeon's caseload are not provided. Still, it should be highlighted that regarding the annual surgeon's caseload, only limited and conflicting data are available. In particular, based on multiple studies, higher surgeon volume does not seem to independently reduce in-hospital mortality [101].

This finding might be explained by the fact that a perioperative multidisciplinary approach is mandatory for patients undergoing RC [180]. It seems that the "total package" of care determines outcomes and, therefore, the hospital volume is the main driver of perioperative outcomes [181].

It should be also acknowledged that data on mortality and morbidity after discharge from the hospital, functional outcomes, rates of readmission, as well as follow-up information are not provided in the GRAND study, limiting the extrapolation of the present findings. Moreover, the Research Data Center excludes variables with fewer than three observations to ensure anonymity and, thus, further outcomes could not be assessed. Finally, all analyses were restricted to data deriving from Germany and, therefore, cannot be applied to other healthcare systems.

8. Conclusions

The present dissertation aimed to examine the German Nationwide Inpatient Data in an attempt to provide a threshold for the RC annual hospital caseload that improves morbidity and mortality and reduces the length of hospital stay and hospital revenues. Based on its findings, hospitals that perform at least 50 RC/year should be considered referral centers, and hospitals that perform at least 70 RC/year should be considered excellence centers. Accordingly, considering that patients who undergo RC in low-volume centers present worse perioperative outcomes, these hospitals should refer patients to centers that reach the minimum requirement of twenty RC/year.

An additional important result of the German administrative data is the fact that the estimated number and severity of perioperative complications were lower compared to other European and Western countries. It should be highlighted that an important proportion of hospitals in Germany reach the minimum recommended thresholds for annual hospital caseload volume. Interestingly, even though the number of RC performed every year increased in Germany in the last years, the perioperative mortality remained stable. Moreover, the COVID-19 pandemic did not negatively affect the number of annual RC and their perioperative outcomes.

Overall, the findings of this dissertation assessing the GRAND study highlight the potential benefits of centralizing bladder cancer care. The latter may not only be useful for patients and hospitals who aim to improve perioperative mortality and morbidity but may also be decisive for healthcare policymakers who aim to reduce the length of hospital stay and the hospital revenues.

Ethics statement: Written informed consent from the participants, as well as ethical approval, was not required for the present study in accordance with the national legislation and institutional requirements. All data used in this work are stored anonymized at the German Federal Statistical Office

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11. Affidavit

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Der Effekt des Krankenhaus-Caseloads auf die perioperative Morbidität und behandlungs-assoziierte Kosten bei der radikalen Zystektomie

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