Systematic Assessment of Complications and Outcome of Radical Cystectomy Undertaken with Curative Intent in Patients with Comorbidity and over 75 Years of Age

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Key Words

Bladder cancer • Muscle-invasive bladder cancer • Radical cystectomy • Complications • Age • Survival • Comorbidity • Ileus

Abstract

Objective: To evaluate the complications, survival and oncological outcome of patients ≥ 75 years of age after radical cystectomy for muscle-invasive bladder cancer. **Patients and Methods:** Between April 1993 and August 2010, 765 patients with muscle-invasive bladder cancer underwent radical cystectomy at one high-volume center. Of these, 70 patients were ≥ 75 years of age. All 70 patients had at least one severe systemic comorbidity with an American Society of Anesthesiologists score of 3. Primary endpoints of this retrospective study were overall and recurrence-free survival with a mean follow-up of 22 months (1–159). Perioperative parameters such as need for blood transfusions, hospital stay, mortality, short- and long-term complications were also assessed. Complications were graded according to the Clavien-Dindo classification. **Results:** Perioperative complications occurred in 23/70 patients (33%) with a 30-day mortality rate of 1.4%. 16/70 patients (23%) developed late complications requiring hospitalization. Within 30 days of surgery, according to the Clavien-Dindo grading, 27% had no complications, 3% grade

1, 49% grade 2, 14% grade 3, 6% grade 4 and 1.4% grade 5 complications. Within 31–90 days after surgery, 76% had grade 1 complications, 3% grade 2, 6% grade 3, 9% grade 4 and 6% grade 4 complications. The calculated 5- and 8-year overall survival rates were 30 and 25%, respectively, with a recurrence-free survival rate of 52% at 5 and 42% at 8 years.

Conclusions: Radical cystectomy is an appropriate and effective treatment for comorbid elderly patients. The oncological long-term outcome is the same as in younger patients while overall survival is comparatively lower. Mortality and complication-related morbidity are comparable to those in younger patients with modern perioperative management.

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Introduction

The incidence of bladder cancer is correlated with age, and muscle-invasive bladder cancer is best treated by radical cystectomy. In addition, the global population is ageing rapidly. In 1950, the group aged 65 years and older accounted for only 5.2% of the world's population but by 2050 this group will account for 16.4%. In the USA this age group will make up 22% of the population [1]. This inevitable ageing of the population will lead to an increase in the number of patients presenting with muscle-

invasive bladder cancer and noticeable comorbidities at an advanced age [2].

Radical cystectomy with pelvic lymph node dissection is oncologically the most effective standard curative treatment modality for muscle-invasive bladder cancer. However, radical cystectomy is associated with considerable postoperative morbidity and mortality. These risks must be weighed against those of progressive bladder cancer which inevitably leads to significant morbidity and eventual mortality within a short period of time.

Advances in perioperative anesthetic management and postoperative care together with improved surgical techniques and the implementation of fast-track concepts have made cystectomy a safer procedure in recent years. Traditionally, cystectomy used to be reserved for younger patients but age limits have been questioned, certainly in large-volume centers. This has led to increasingly older patients undergoing radical cystectomy.

However, any benefit from treatment by radical cystectomy must be associated with an acceptable postoperative morbidity and outcome. Thus, as radical cystectomy is a major surgery carrying definite potential risks, the procedure must always be indicated in a balanced risk-benefit assessment which is even more important in elderly and comorbid patients.

Our department is a high-volume center with 60–70 radical cystectomies on average per year. We long ago abandoned any definite age limit for radical cystectomy and base the decision on the assessment of biological age, comorbidity, an individual putative risk-benefit assessment as well as, of course, the patients' wishes. We therefore undertook the evaluation of our results in patients aged 75 years and older. Not surprisingly, all of these patients had significant comorbidities.

Patients and Methods

Between April 1993 and August 2010, 765 patients with muscle-invasive bladder cancer underwent radical cystectomy with urinary diversion at the Department of Urology of Dresden University Hospital. Of these 765 patients, 70 were ≥ 75 years of age (mean 78.8, median 78, range 75–90; 48 males and 22 females) and had at least one severe comorbidity [American Society of Anesthesiologists (ASA) score with physical status class 3]. For more specific comorbidity assessment, all patients were additionally categorized according to the Charlson Index Score (CIS) [3].

In all 70 patients, radical cystectomy was performed with curative intent as a cystoprostatectomy in males including the prostate and seminal vesicles and inclusive of the uterus, adnexa, anterior vaginal wall and urethra in females. According to the in-house standard, radical cystectomy with curative intent is always

performed with an extended pelvic lymphadenectomy up to the aortic bifurcation and average lymph node counts were above 20.

For the purposes of this assessment, perioperative complications were defined as any adverse event within 30 days of surgery and perioperative mortality was defined as death from any cause within 30 days of surgery. A late complication was defined as any complication noted more than 30 days after surgery. For this retrospective assessment, patient data were retrieved from hospital medical records and outpatient urology files. The mean follow-up was 22 months (range 1–159). Internal review board approval was obtained for this retrospective data analysis.

Overall survival and disease-free survival were analyzed by Kaplan-Meier statistics from the date of cystectomy. Patients alive were censored at the time of the last follow-up. Likewise, time to recurrence was defined as the time from surgery to the first diagnosis of recurrence. For the comparison of hospital stay the χ^2 test was used with the significance level set at $p < 0.05$.

Results

Comorbidities

Cardiological disease, diabetes, obesity, renal insufficiency and respiratory diseases were the most common comorbid conditions (table 1). 23 patients (33%) had three or more comorbidities. All 70 patients were classified as ASA 3. Thus, although all patients had significant comorbidity according to the ASA definition, 11/70 patients (16%) had no classified comorbidity according to the Charlson definition (CIS = 0). A CIS of 2 or greater was observed in 37/70 patients (53%) (fig. 1).

Perioperative Parameters

Mean operative time was 4.6 ± 1.0 h (median 4.4), average intraoperative blood loss collected by suction was 1,135 ml. 44 of the 70 patients (63%) received blood transfusions intraoperatively and/or postoperatively: 34% during (mean 1.5 ± 1.7 units) and 56% after surgery (mean 2.9 ± 1.3 units).

The average hospital stay was 18.9 ± 6.2 days (median 16). Hospital stay was significantly longer if complications occurred: 23.1 ± 11.7 days (median 17) with complications versus 16.8 ± 3.2 (median 15) without ($p < 0.05$).

Surgery and Pathological Results

Two male patients underwent simultaneous urethrectomy for positive urethral margins. Urinary diversions in these 70 patients were mostly ileal conduits (86% of patients), cutaneoureterostomies in 7 patients (10%), an ileal neobladder in 2 and bilateral nephrostomies in 1 patient. According to the in-house protocol, ureters were stented by mono-J stents until postoperative day 11 [4]. The tumor characteristics of the patients are given in table 2.

Fig. 1. Distribution of CIS for the patient cohort.

Early Complications

A total of 23/70 patients (33%) developed one or more perioperative complications (table 3). 18 out of 70 patients (26%) had only one complication, while 5 patients (7%) had two or more perioperative complications.

We classed complications into 'medical' and 'surgical', e.g. pneumonia versus wound infection (table 3). For the definitions of complications we used see the legend to table 3. The most frequent medical complication was paralytic ileus in 6 patients, all of whom were managed conservatively. Septicemia occurred in 3 patients and antibiotics-induced enterocolitis in another 3 patients. The most common surgical complication was superficial wound breakdown with secondary wound healing in 9 patients (13%). Revision laparotomies were done in 2 patients, one for small bowel obstruction and one for secondary bleeding with an extensive pelvic hematoma. Three patients (4%) underwent surgical revision for complete fascial wound dehiscence. The overall reoperation rate was 7%. One 83-year-old patient died on postoperative day 4 due to septicemia. This gives a 30-day mortality rate of 1.4% for this group of 70 patients.

Late Complications

Sixteen patients of the remaining 69 patients (23%) developed late postoperative complications which needed hospitalization after the 30-day period following surgery (table 3). 88% of these late complications developed during the first postoperative year. Eight patients (11%) developed surgical complications, which included parasto-

Table 1. Prevalence of the most frequent concomitant diseases

Comorbidity	
Hypertension	47 (67%)
Diabetes	26 (37%)
Coronary heart disease	25 (36%)
Renal insufficiency	14 (20%)
COPD	12 (17%)
Cerebrovascular disease	8 (11%)
Obesity	6 (9%)
Peripheral vascular disease	5 (7%)

Definitions of comorbidities: hypertension: at least stage 1 hypertension (American Heart Association classification) with at least one antihypertensive drug for more than 3 months; diabetes: long-term treatment with oral anti-hyperglycemic agent or insulin; coronary heart disease: with coronary stents or history of coronary artery bypass or myocardial infarction, or two episodes of angina pectoris with long-term medication with at least one specific drug (nitroglycerin, β -blockers, calcium channel blockers or ACE inhibitors); renal insufficiency: glomerular filtration rate <60 ml/min/1.73 m² for at least 3 months; COPD: confirmed by spirometry, on long-term medication with bronchodilators and/or corticosteroids; cerebrovascular disease: history of cerebral infarction or intracranial hemorrhage; obesity: BMI >30 ; peripheral vascular disease: intermittent claudication at least stage II Fontaine classification.

Table 2. Local tumor and regional nodal stage distribution

Tumor stage		
Before cystectomy	pTa	1.4%
	pT1	8.6%
	pTis	8.6%
	pT2	61.4%
	pT3	20.0%
After cystectomy	pT0	2.9%
	pT1	15.7%
	pT2	18.6%
	pT3	41.4%
	pT4	11.4%
	pTis	10.0%
Nodal status		
	pN0	74.9%
	pN1	11.4%
	pN2	15.7%

mal hernia in 3 patients. Five patients developed complications which required surgical intervention during the first postoperative year: 1 with uretero-ileal anastomotic stenosis requiring ureteral reimplantation, 1 incisional hernia, 1 enteric fistula, 1 large pelvic lymphocele requiring percutaneous drainage and 1 conduit reimplantation

Table 3. Early complications (0–30 days after surgery) and late postoperative complications (31–90 days after surgery)

Perioperative complications, n (%)	
Medical	
Deep venous thrombosis	1 (1.4)
Pulmonary embolism	1 (1.4)
Septicemia	3 (4.3)
Paralytic ileus	6 (8.6)
Acute respiratory distress	1 (1.4)
Enterocolitis	3 (4.3)
Mortality	1 (1.4)
Surgical	
Small bowel obstruction	1 (1.4)
Pelvic lymphocele	3 (4.3)
Secondary wound healing/wound dehiscence	9 (12.9)
Pelvic hematoma with revision	1 (1.4)
Total patients with perioperative complications	23 (32.9)
Late postoperative complications after 30 days, n (%)	
Urinary tract infection	4 (5.7)
Parastomal hernia	3 (4.3)
Subileus	2 (2.9)
Severe hydronephrosis	1 (1.4)
Incisional hernia	1 (1.4)
Uretero-ileal anastomosis stenosis	1 (1.4)
Enteric fistula	1 (1.4)
Pelvic lymphocele	1 (1.4)
Severe hyperchloremic acidosis	1 (1.4)
Stomal dermatitis	1 (1.4)
Total patients with late complications	16 (22.9)

Definitions of perioperative complications: deep venous thrombosis: formation of clot within vein requiring treatment; pulmonary embolism: clinical evidence of pulmonary embolism; septicemia: acutely ill with positive blood culture or proven toxemia; paralytic ileus: postoperative vomiting associated with abdominal distension requiring cessation of oral intake and/or nasogastric tube or the intolerance of oral intake by postoperative day 5 with a lack of bowel activity without signs of small bowel obstruction; acute respiratory distress: severe respiratory insufficiency requiring unplanned intubation and assisted respiration; myocardial infarction: new transmural infarction as demonstrated by Q waves on electrocardiogram; enterocolitis: persistent diarrhea >2 days and/or detection of *Clostridium difficile* toxin in stool; small bowel obstruction: mechanical bowel obstruction requiring surgical intervention; pelvic lymphocele: pelvic fluid collection of more than 50 ml on ultrasound with percutaneous drainage performed if significant venous compression seen on Doppler ultrasound and/or unilateral leg edema and/or leg pain and/or diagnosed deep venous thrombosis; pelvic hematoma: transfusion need >4 units during the first 72 postoperative hours; intestinal anastomotic insufficiency: clinical and/or imaging diagnosis insufficiency of small bowel anastomosis suspected or diagnosed with surgical intervention; urinary anastomotic insufficiency: uretero-ileal anastomotic leakage and/or retroperitoneal urinoma diagnosed with need for intervention; secondary wound healing: superficial wound infection with/without wound breakdown and conservative treatment; wound dehiscence: wound breakdown with disruption of fascial suture requiring surgical repair.

Fig. 2. Kaplan-Meier estimates for overall and recurrence-free survival after radical cystectomy in the patient cohort.

for treatment-refractory parastomal dermatitis. Late medical complications responsive to conservative treatment occurred in 8 of the remaining 69 patients (11%) and consisted of upper urinary tract infections in 4 cases, acute renal failure in 1, metabolic acidosis in 1 and subileus in 2 patients.

Clinical Follow-Up

Overall, 44/69 patients (64%) died during follow-up (median 22 months, range 1–159). 21 patients (30%) died of noncancer causes and 23 (33%) from recurrent and progressive bladder cancer. 37 out of 44 deaths (84%) occurred during the first 3 years (20 due disease progression, 17 due to other causes).

With the mean follow-up just under 2 years, Kaplan-Meier statistics yielded projected overall survival rates of 30% for 5 years and 25% for 8 years. The respective calculated recurrence-free survival rates were 52% at 5 years and 42% at 8 years (fig. 2).

Discussion

Radical cystectomy is the standard treatment for patients with muscle-invasive bladder cancer. The contemporary mortality and morbidity of this procedure is clearly lower than it was in previous decades. This is probably due to more sophisticated peri- and postoperative handling, including improved anesthetic and surgical man-

Table 4. Clavien-Dindo grading of postoperative complications

Clavien-Dindo grade	Days 0–30	Days 31–90	Days 91–365
0	27%	76%	92%
1	3%	3%	3%
2	49%	6%	1%
3	14%	9%	3%
4	6%	6%	1%
5	1.4%	0%	0%

Summary of complications by the highest grade experienced by each patient. Clavien-Dindo classification: grade 0: no event observed; grade 1: use of oral medication or bedside intervention; grade 2: use of intravenous medication, total parenteral or enteral nutrition, blood transfusion; grade 3: interventional radiology, therapeutic endoscopy, intubation, angiography, surgery; grade 4: residual or lasting disability requiring major rehabilitation or organ resection; grade 5: death of patient.

agement. However, postoperative morbidity after radical cystectomy remains very considerable with over 30% in the early postoperative period [5, 6]. Elderly patients have long been recognized as a high-risk group for complications, with age and high comorbidity being important factors for surgical outcome, especially postoperative morbidity.

On the other hand, insufficiently treated muscle-invasive bladder cancer will lead to high morbidity due to local and/or systemic progression, with repeated hospitalizations and eventual death. Thus, progressive bladder cancer will inevitably impact severely on the patients' quality of life. Therefore, potentially curative treatment should not be withheld on the grounds of age alone.

It needs to be considered that age correlates with comorbidity – older adults are more likely to have one or more chronic systemic diseases [7–9]. In this study we evaluated the outcome of radical cystectomy undertaken for curative intent in old patients with comorbidity, i.e. at least one severe systemic disease (ASA 3). Thus, in this cohort of patients over 75 years of age, 68% of the patients had hypertension, 38% diabetes and 35% coronary heart disease. One third of this group suffered from three or more systemic comorbidities.

In these patients thus characterized by age and comorbidities, the overall rate of perioperative complications was 33%. Other recent reports on radical cystectomy in elderly patients have reported a wide range of complication rates [10]. May et al. [11] reported an early overall complication rate of 38.6% in patients ≥ 75 years of age,

Yamanaka et al. [12] reported a rate of 30.6% in patients over 80 years of age, and Gamé et al. [13] reported a rate of 64% (early complications). Sogni et al. [14] reported that the complication rates in patients ≥ 75 years of age depended on the type of urinary diversion used, with an overall early complication rate of 30.8% with orthotopic neobladders compared to 21.7% with ileal conduits.

The average number of blood units transfused was 1.7 per patient in our series (average measured blood loss was 1,135 ml). This compares with other series [15–18] with average transfusion requirements between 1.3 and 3.2 units per patient. However, 63% of our patients received blood transfusions while others have reported lower transfusion proportions for their series of cystectomy patients aged 75 years or older, ranging between 39 and 65% of patients [15, 16, 18, 19]. The relatively high transfusion rate in our series may be due to the also relatively high comorbidity status of our patients.

The average hospital stay after radical cystectomy in the literature ranges between 7 and 34 days [13, 15–20]. This is largely dependent on the health care systems involved, with much shorter hospital stays in the US compared to European countries [13, 15–17, 20]. Thus, comparisons are only meaningful within the same health care system. The mean hospital stay in our series was 19 days and was significantly prolonged if complications occurred, a finding also reported by others [13, 15, 16, 19]. In our study, the occurrence of a complication led to a prolongation of the hospital stay by 6.3 days on average.

One of the most common postoperative complications after radical cystectomy with urinary diversion is ileus. The ileus rate was comparatively low in our series compared to the literature [12, 15, 21–23]. We believe that this is due to our routine use of 'fast track' principles, i.e. avoiding extensive preoperative bowel preparation and using early bowel stimulation. Early bowel stimulation in our protocol includes removal of the nasogastric tube with extubation, first mobilization on the evening of surgery, oral intake from day 1 and postoperative analgesia by high thoracic epidural anesthesia with an opioid plus a local anesthetic, which reduces sympathetic input to the small bowel and thus improves motility.

Are comorbidities risk factors for complications? It must be considered that some comorbidities have a detrimental influence on physiological functions, which directly affects postoperative recovery. For example, bowel function may already be impaired in patients with hypertensive and/or diabetic vasculopathy and neuropathy. Boström et al. [24] reported that an ASA ≥ 3 , age and several comorbidities were significant risk factors for the

rate of major complications in their series. In a large series, Hautmann et al. [25] reported four significant predictors for an increased rate and severity of early complications after radical cystectomy and these were ASA and CIS, age and tumor stage. Hollenbeck et al. [26] also identified several independent risk factors for postoperative morbidity: age, a history of dyspnea, chronic steroid use and an ASA ≥ 3 . Similarly, March et al. [27] identified age and cardiac disease as independent risk factors for major complications. Zebic et al. [16] reported ASA 4 as a significant risk factor for mortality while complications and mortality were not different between ASA 2 and ASA 3 in their series. Also, in a prospective study by Wolters et al. [28] which looked at the influence of ASA status on postoperative outcome, an ASA score ≥ 3 was identified as a significant predictor for complications. Thus, most studies identify patient comorbidity as an important risk factor for complications after radical prostatectomy. Importantly, obesity by itself does not seem to be an independent risk factor [29].

The most severe complication is mortality. Reported mortality rates after radical cystectomy in patients ≥ 75 years range between 0 and 9.5%, depending on the size of the series and the defined postoperative period (in-house, 30 or 90 days) [11–21, 30, 31]. Thus, Chang et al. [17] reported 0% mortality in 44 patients (≥ 75 years with ASA ≥ 3) in 2001, and 12.7% 90-day overall mortality in 2011 (169 patients >75 years of age) [31]. Deliveliotis et al. [18] reported one death in 54 patients (≥ 75 years with ASA ≥ 3), Gamé et al. [13] a 4% mortality in patients ≥ 75 years, Serra et al. [21] a rate of 5% and Sogni et al. [14] 5.9%. Morgan et al. [31] reported a 30-day mortality rate of 7% in patients over 75 years of age and Madersbacher et al. [2] a 60-day mortality of 5.2% in patients aged 80 years or older. Considering just the 90-day mortality, rates of 6.8% in patients aged 80 years or older compared to 2.2% in younger patients have been reported by Donat et al. [20], while Chang et al. [6] reported 12.7%. In our study, the 90-day mortality rate was 1.4%.

In a large series with 1,072 consecutive patients, Clark et al. [32] retrospectively analyzed outcome and mortality of radical cystectomy across age groups. Mortality was 0% in the <60 -year-old age group and 4% in the >80 -year-old age group, although this was statistically not significant.

The rate of late complications in elderly patients (23% in our study) has been reported between 16.4 and 42% and several studies have identified the type of urinary diversion as a major risk factor [11–13, 15, 18, 30]. The most frequent late postoperative complications reported

are chronic/recurrent upper tract infections (5.1–13.8%), stomal complications (4.3–20.4%), incisional hernia (4.1–7.4%) and metabolic disturbances [12, 15, 18, 21, 33].

Does comorbidity affect long-term survival after radical cystectomy? A study from the Alberta Urology Institute radical cystectomy database examined this question and reported that comorbidity was independently associated with both overall as well as cancer-specific mortality [34]. They reported a 5-year overall survival rate of 47% for patients with severe comorbidity and a mean age of 66 years. This may be compared with the 5-year overall survival of 30% in comorbid elderly patients in our series. While cancer-specific survival is foremost influenced by tumor stage [35], it also seems to depend on comorbidity.

Our study has several limitations. It is entirely retrospective and covers a large time span. The sample size is relatively small and there is a selection bias in that patients with more severe comorbidity and with an inappropriately high perioperative risk were of course excluded from radical cystectomy. Despite these obvious limitations we believe that our study adequately represents reliable data on results in elderly and comorbid patients selected for radical cystectomy with curative intent by urologic surgeons working in high-volume centers.

Conclusions

Our experience suggests that radical cystectomy can be a safe and effective procedure in elderly patients who also have severe impairments due to comorbidities common in this age group. While neither age nor comorbidities are valid reasons to withhold potentially curative treatment from a patient who wants to be cured, age and certain comorbidities (respiratory, cardiac) as well as the type of urinary diversion are significant risk factors for postoperative complications.

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