The impact of minimal invasive surgery on early complications and mortality after radical cystectomy for muscle-invasive urothelial bladder cancer

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Summary

Purpose: To evaluate the 30-day death rate and the factors associated with short-term complications after radical cystectomy for muscle-invasive urothelial bladder cancer.

Methods: The study included 123 patients (age 64.1±7.9 years; 111 (90.2%) males and 12 (9.8%) females) previously diagnosed with urothelial bladder cancer, admitted for radical cystectomy in a tertiary center. The following data were noted: age, gender, perioperative chemotherapy and radiotherapy, pre- and postoperative hemoglobin and creatinine levels, tumor stage, type of surgery, type of diversion and Clavien classification. Patients were followed for 30 days and several complications were noted: cardiovascular, gastrointestinal, local, or infectious complications, anemia. Death rate was also recorded.

Results: Open cystectomy was performed in 81 (65.9%) patients, and laparoscopic approach was used in 43 (34.1%) patients. An ileal neobladder was created for 11 (8.9%) patients and noncontinent diversion for 112 (91.1%). There were 2 (1.6%) deaths following surgery. The following complication rates were noted: 27 local (22%), 16 infectious (13%), 54 cases of postoperative anemia (43.9%). Postoperative anemia was independently associated with open cystectomy (OR, 5.7; p=0.001), ileal neobladder (Odds ratio/OR, 14.6, p=0.002) and male gender (OR, 0.15, p=0.01). The Clavien classification did not differ between open and laparoscopic cystectomy (p=0.3), even though the complication grade was higher in the former.

Conclusion: The 30-day death rate after radical cystectomy for muscle-invasive urothelial bladder cancer was low. Open cystectomy was associated with more severe short-term complications as compared with the laparoscopic approach. Postoperative anemia was associated with the type of surgery, diversion type and male gender.

Key words: complications, radical cystectomy, urothelial bladder cancer

Introduction

Urothelial bladder cancer is the most common cancer affecting the urinary tract. It is more frequent in developed countries, and according to GLOBOCAN, there were about 430,000 new urothelial bladder cancer cases in 2012. In Romania, the incidence is 27.4 per 100,000 people, which is very close to the incidence recorded in the European Union (EU), i.e. 29.1 per 100,000 people. The mortality in Romania is one of the highest in EU (9.9 per 100,000 people), as compared with the average mortality in EU (8.4 per 100,000 people). Urothelial bladder cancer is also 3-fold higher in men [1].

Approximately 75% of new urothelial bladder cancer cases are diagnosed in early stage, without

the invasion of the bladder muscle layer [2]. Muscle-invasive form of urothelial bladder cancer represents 25% of bladder cancers. The patient's age and the overall health status influence the choice of management and the type of urinary diversion. Radical cystectomy with pelvic lymph node dissection with reconstruction of the urinary tract is the standard procedure when dealing with muscle-invasive urothelial bladder cancer or non-muscle invasive urothelial bladder cancer with a very high risk or BCG failure [3,4]. Systemic chemotherapy combined with radiotherapy is an alternative in patients that are not candidates for radical surgery [4].

Two major techniques are used for radical cystectomy: open cystectomy and laparoscopic cystectomy (with or without robotic-assistance). A metanalysis showed that patients who underwent open cystectomy were older than in the case of laparoscopy. The operative times were longer for patients with laparoscopy, but with fewer days of hospital stay and less blood loss. Open cystectomy was associated with more perioperative complications [5]. The short-term complications are directly related to surgery and include local (wound) complications, infectious complications and gastrointestinal complications [6]. Blood loss is relatively high in these patients on average from (range 560 ml to 3,000 ml), which leads to transfusions that can be linked to major complications [7-9].

The aim of this study was to evaluate the 30-day death rate and the factors associated with short-term complications after radical cystectomy for muscle-invasive urothelial bladder cancer.

Methods

This was a prospective, longitudinal, analytic, observational, cohort study. The study included 123 patients that were previously diagnosed with urothelial bladder cancer, admitted for radical cystectomy at the Department of Urology of the Municipal Clinical Hospital in Cluj-Napoca, between July 2011 and April 2015. The patients signed informed consent form for inclusion in the study. The study protocol was in accordance with the Helsinki Declaration of 1975, as revised in 2000, and was approved by the Ethics Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy.

The inclusion criteria were the diagnosis of muscle-infiltrating urothelial bladder cancer or non-muscle invasive urothelial bladder cancer with high risk of progression (T1 high grade/G3, carcinoma *in situ* being BCG-refractory, recurrence after BCG treatment, papillary tumors that were not resolved using endoscopy), requiring radical cystectomy according to the guidelines, and patient age over 18 years [4].

The following patients were excluded from the study: patients that did not sign informed consent form,

Table 1. Surgery related data

Variables	n (%)
ASA score	
1	6 (4.9)
2	60 (48.8)
3	50 (40.7)
4	7 (5.7)
Preoperative chemotherapy	27 (22)
Postoperative chemotherapy	41 (33.3)
Preoperative radiotherapy	5 (4.1)
Postoperative radiotherapy	6 (4.9)
Preoperative hemoglobin (g/dl)	12±1.8
Postoperative hemoglobin (g/dl)	9.6±1.4
Preoperative creatinine (mg/dl)	1.1 (1-1.5)
Postoperative creatinine (mg/dl)	1 (0.8-1.2)
TNM stage	
Stage 0a	6 (4.8)
Stage 0is	5 (4)
Stage I	23 (18.7)
Stage II	36 (29.3)
Stage IIIa	28 (22.8)
Stage IIIb	22 (17.9)
Stage IVa	3 (2.4)
TNM stage	
0-II	70 (56.9)
III-IV	53 (43.1)
Type of surgery	
Open cystectomy	81 (65.9)
Laparoscopic cystectomy	42 (34.1)
Overall operation time (min)	250 (230-290)
Diversion type	
Ileal neobladder	11 (8.9)
Noncontinent	112 (91.1)
Estimated blood loss (ml)	610 (450-780)
Transfusion (yes)	57 (46.3)
Inpatient stay (days)	11 (8-13)
ICU stay (days)	4 (2-5)
Return to OR within 30 days	11 (8.9)
Postoperative anemia	54 (43.9)
Cardiovascular complications	10 (8.1)
Gastrointestinal complications	15 (12.2)
Local complications	27 (22)
Infectious complications	16 (13)
No complications	27 (22)
Clavien classification	
Grade I	36 (29.3)
Grade II	49 (39.8)
Grade IIIb	7 (5.7)
Grade IVa	3 (2.4)
Grade V	1 (0.8)
Deaths	2 (1.6)

patients with non-urothelial carcinoma, and patients with indication for cystectomy but with severe cardiorespiratory comorbidities.

The following demographic, anamnestic and clinical data were recorded: age, gender, body mass index (BMI), smoking status, history of cardiac diseases. Disease and surgery related data included ASA score, postoperative chemotherapy and radiotherapy, pre- and postoperative hemoglobin levels (12-16 g/dl for women, 13-16.5 g/dl for men), creatinine levels (normal values 0.8-1.2 mg/dl), tumor stage, type of surgery, type of diversion, total duration of intervention, estimated blood loss, need for transfusion, ICU stay, inpatient stay and the need for re-intervention. Neoadjuvant chemotherapy was proposed to patients with clinically nonmetastatic disease.

The surgical technique included removal of the prostate in male patients, while female patients underwent hysterectomy and bilateral ovariectomy if those organs were present. We used a standardized lymph node dissection including obturator, external, internal and common iliac and presacral nodes. Intraoperative frozen section analysis of the lymph nodes was not performed. Open radical cystectomy was performed using a midline transperitoneal approach. Laparoscopic surgery was performed in a standard manner or robotic-assisted using the da Vinci SI HD surgical system (Sunnyvale,CA). A transperitoneal 5-port technique was used for the laparoscopic approach. The robotic-assisted radical cystectomy (RARC) was performed using a 6-port transperitoneal approach (4 ports for the robotic arms and 2 ports for the laparoscopic table side assistance). In case of laparoscopic or robotic technique the urinary diversion was performed extracorporeally via a small median laparotomy. In some cases of RARC, the urinary diversion was performed using a completely intracorporeal technique.

Patients were followed for 30 days and the following complications were registered: cardiovascular, gastrointestinal, local or infectious complications, anemia. The Clavien classification was calculated. Mortality was also recorded.

Statistics

Statistical analyses were performed using Med-Calc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Qualitative data were expressed by frequency and percentage and quantitative data were described using mean±standard deviation or median and interquartile range, when appropriate. Comparison between groups was performed using the chi-square test, Student's t-test or Mann-Whitney U test, when appropriate. Area under the receiver operating characteristic curve (AUROC) was used to calculate a cut-off value for creatinine regard-

Table 2. Parameters associated with postoperative anemia at 30 days

Parameters	Postoperative anemia n (%)	Without postoperative anemia n (%)	p
Age, years	66 (60.5-70)	64 (58.5-70)	0.30
Gender			0.04
Female	9 (16.7)	3 (4.3)	
Male	45 (83.3)	66 (95.7)	
BMI (kg/m²)	26 (24-27)	25 (23.5-28)	0.90
Preoperative anemia	43 (51.8)	11 (27.5)	0.01
Preoperative creatinine (mg/dl), median (range)	1.2 (1-1.84)	1.09 (0.99-1.26)	0.06
Postoperative creatinine (mg/dl), median (range)	1.02 (0.86-1.33)	1 (0.89-1.13)	0.30
ASA score			0.40
1	3 (5.6)	3 (4.3)	
2	22 (40.7)	38 (55.1)	
3	25 (46.3)	25 (36.2)	
4	4 (7.4)	3 (4.3)	
Diversion type			0.05
Ileal neobladder	8 (14.8)	3 (4.3)	
Noncontinent	46 (85.2)	66 (95.7)	
Type of surgery			0.002
Open cystectomy	44 (81.5)	37 (53.6)	
Laparoscopic	10 (18.5)	32 (46.4)	
TNM stage III-IV	29 (54.7)	25 (35.7)	0.06
Preoperative chemotherapy	11 (20.4)	16 (23.2)	0.80
Preoperative radiation	2 (3.7)	3 (4.3)	01/01/00
Postoperative chemotherapy	21 (38.9)	20 (29)	0.30
Postoperative radiation	2 (3.7)	4 (5.8)	0.60

ing the presence of postoperative anemia (the value was chosen when sensitivity and specificity were highest). Multivariate analysis was performed by binary logistic regression in order to find out the independent parameters associated with anemia. A p value <0.05 was considered statistically significant.

Results

The mean age of patients was 64.1±7.9 years. There were 111 (90.2%) males and 12 (9.8%) females, with a mean BMI of 26 (range 24-27) kg/m². History of cardiac diseases was present in 98 (79.7%) patients, and 72 (58.5%) were smokers.

Surgery related data are described in Table 1. Open radical cystectomy was performed in 81 (65.9%) patients. Laparoscopic surgery was performed as a standard method in 28 (22.8%) patients or robotically-assisted using the da Vinci SI HD surgical system in 14 (11.4%) patients. The following complications were observed: gastrointestinal (ileus 11; 8.9% cases, enteric fistulas 4; 3.3% cases, diarrhea 3; 2.4% cases); infection with *Clostridium dificille* 3; 2.4% cases, pyelonephritis 15; 12.2% cases, sepsis 5; 4.1% cases, local (wound dehiscence 5; 4.1% cases, abdominal incisional hernia 3; 2.4% cases, and seroma 9; 7.3% cases).

The Clavien classification did not differ between open and laparoscopic cystectomy (p=0.3), even though the complication grade was higher

Table 3. Multivariate analysis for presence of postoperative anemia at 30 days

Variables	B	P	OR	95% C.I. for OR	
				Lower	Upper
Male gender	-1.83	0.018	0.16	0.03	0.73
Preoperative anemia	0.64	0.2	1.91	0.66	5.52
Preoperative creatinine >1.34 mg/dl	1.46	0.002	4.33	1.68	11.12
Ileal neobladder	2.94	0.001	18.93	3.15	113.45
Open cystectomy	1.63	0.003	5.12	1.75	14.96

Table 4. Parameters associated with local complications at 30 days

Parameters	Local complications n (%)	Without local complications n (%)	p
Age, years	64 (58-70)	65 (59-70)	0.60
Gender			1.00
Female	2 (7.4)	10 (10.4)	
Male	28 (92.6)	86 (89.6)	
BMI (kg/m²), median (range)	26 (24-29)	25.5 (23.2-27)	0.20
Preoperative creatinine (mg/dl), median (range)	1.03 (0.95-1.39)	1.17 (1-1.5)	0.10
Postoperative creatinine (mg/dl), median (range)	1 (0.78-1.12)	1 (0.9-1.22)	0.40
ASA score			0.80
1	1 (3.7)	5 (5.2)	
2	12 (44.4)	48 (50)	
3	13 (48.1)	37 (38.5)	
4	1 (3.7)	6 (6.2)	
Diversion type			0.70
Ileal neobladder	3 (11.1)	8 (8.3)	
Noncontinent	24 (88.9)	88 (91.7)	
Type of surgery			0.40
Classic	20 (74.1)	61 (63.5)	
Laparoscopic	7 (25.9)	35 (36.5)	
TNM stage III-IV	11 (20.8)	16 (22.9)	0.90
Preoperative chemotherapy	5 (18.5)	22 (22.9)	0.80
Preoperative radiation	2 (7.4)	3 (3.1)	0.30
Postoperative chemotherapy	10 (37)	31 (32.3)	0.30
Postoperative radiation	2 (7.4)	4 (4.2)	0.60

in the former. Moreover, the complication grade was higher in noncontinent diversion than in ileal neobladder, but the difference was not statistically significant (p=0.1).

Postoperative anemia was associated with female gender, preoperative anemia, higher preoperative creatinine blood levels, continent diversion and open cystectomy (Table 2). A cut-off value was calculated for creatinine over which the chance of anemia increased: 1.34 mg/dl (AUC 0.596; 95% CI 0.503 to 0.683); sensitivity 48.15; 95% CI 34.3 - 62.2), specificity 79.71; 95% CI 68.3 - 88.4; p=0.07).

Patients that underwent laparoscopic surgery lost less blood than those with open cystectomy (mean 380, (range 317-582) ml vs. mean 710, (range 595-870) ml; p<0.001). The diversion type did not influence the estimated blood loss (p=0.2).

Binary multivariate regression was used in order to find out which variables were independently associated with postoperative anemia (Table 3). Continent diversion (ileal neobladder) and open cystectomy were the variables with the highest probability to be associated with postoperative anemia. Male gender was less likely to develop anemia.

No variables that were more likely to determine local complications were found (Table 4).

No variables that were more likely to determine infectious complications were found (Table 5).

Discussion

This study showed the incidence of complications and the death rate 30 days after radical cystectomy for muscle-invasive urothelial bladder cancer in a single tertiary center. The parameters that influenced the appearance of short-term complications were also evaluated. Variables statistically significantly linked with postoperative anemia alone were found.

The death rate 30 days after surgery was very low in our study, only 1.6%. The mortality rate was slightly lower than data reported in the literature. This might be related to the low number of severe complications in our study. Shabsigh et al. reported a death rate at one month of 2.3% (including inpatient mortality) [6]. Chahal et al. found a mortality rate at 30 days of 3.1% [10]. Another study found an overall mortality rate at 30 days of 2.8% [11]. The 30-day mortality rate in our study was lower, but comparable with the one (1.9%) from hospitals with high numbers of cystectomies (>20 cases/year) [12]. A high frequency of cystectomies is as-

Table 5. Parameters associated with infectious complications at 30 days

Parameters	Infectious complications n (%)	Without infectious complications n (%)	p
Age, years, median (range)	66 (58.2-69.7)	64 (59-70)	0.90
Gender			0.10
Female	3 (18.8)	9 (8.4)	
Male	13 (81.2)	98 (91.6)	
BMI (kg/m²), median (range)	24.5 (22-26.7)	26 (24-28)	0.10
Preoperative creatinine (mg/dl), median (range)	1 (0.8-1.35)	1.17 (1-1.5)	0.10
Postoperative creatinine (mg/dl), median (range)	1.05 (0.94-1.19)	1 (0.87-1.23)	0.70
ASA score			0.40
1	2 (12.5)	4 (3.7)	
2	8 (50)	52 (48.6)	
3	5 (31.2)	45 (42.1)	
4	1 (6.2)	6 (5.6)	
Diversion type			0.60
Ileal neobladder	2 (12.5)	9 (8.4)	
Noncontinent	14 (87.5)	98 (91.6)	
Type of surgery			1.00
Classic	11 (68.8)	70 (65.4)	
Laparoscopic	5 (31.2)	37 (34.6)	
TNM stage III-IV	6 (11.3)	10 (14.3)	0.80
Preoperative radiation	1 (6.2)	4 (3.7)	0.30
Postoperative chemotherapy	4 (25)	37 (34.6)	0.60
Postoperative radiation	1 (6.2)	5 (4.7)	0.50

sociated with superior experience, hence a lower mortality rate.

Open cystectomy was associated with more complications than the laparoscopic approach, although only anemia was statistically significant more frequent. Some studies found that the 30-day complication rate did not differ between open cystectomy and laparoscopic cystectomy, but open cystectomy was associated with more severe complications [13]. Our study results were in partial agreement with Bochner et al., as the frequency of high-grade complications (3-5 Clavien class) was below 10%, as compared to the one in their study (21%). This might be explained partially by the lower estimated blood loss in our study in the laparoscopic group, while the hemorrhage from the open cystectomy group was comparable with the ones in their study.

The prevalence of postoperative anemia was high in our study as compared with other studies (43.9%). DiLizia et al. reported a prevalence of 7.2% in patients that underwent robotic-assisted radical cystectomy, which is still higher than the one in our laparoscopic group (18.5%). Even though blood loss was similar in both studies, the difference lies in the prevalence of preoperative anemia that was higher in our study due to the more advanced cancer stage [14]. Postoperative anemia was linked to several independent parameters: open cystectomy, ileal neobladder, high creatinine, and gender. Open cystectomy is usually associated with higher blood loss than the laparoscopic procedure. In our study, blood loss volume was almost double in patients with open cystectomy, as compared to the laparoscopic group. The likelihood of postoperative anemia was almost six (5.7) times higher in the open cystectomy group, which means that blood loss is not the only important factor. Male patients were less likely to develop anemia than female patients, even if the gender ratio was 9.2:1. The rate of postoperative anemia was higher in women probably because the cancer was more advanced locally and

the surgical technique required hysterectomy to be performed, which is an operation rarely conducted by urologists [15].

The frequency of gastrointestinal and local complications was higher than those described in other studies. Zakaria et al. reported that 4.6% of patients developed gastrointestinal tract complications and 5.5% wound complications [16]. The rate of local complications in the study conducted by Shabsigh et al. was lower than in our study (15%) [6]. Other studies found a much higher rate of gastrointestinal complications (29%), almost double than in the present study. In a multicentric study, Johar et al. observed that 27% of patients had gastrointestinal complications and 23% infections, higher than in our study, even though their study included only patients that underwent robot-assisted radical cystectomy [16].

The present study has some limitations: the moderate number of patients included in the study; data reflect the experience of one tertiary center; not all patients could be followed for 90 days after surgery.

The strength of our study derives from the fact that the mortality and complications rates were very low, even though almost half of patients were in the stage III or IV.

Conclusions

The 30-day death rate following radical cystectomy for muscle-invasive urothelial bladder cancer was low. Open cystectomy was associated with more severe short-term complications as compared with the laparoscopic approach. Postoperative anemia was associated with the type of surgery, diversion type and male gender.

Conflict of interests

The authors declare no conflict of interests.

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