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Introduction

Standardized methods of reporting complications after radical cystectomy (RC) and urinary diversions (UD) are necessary to evaluate the morbidity associated with this operation to evaluate the modified Clavien classification system (CCS) in grading perioperative complications of RC and UD in a real life cohort of patients with bladder cancer.

Materials and methods

A consecutive series of patients treated with RC and UD from April 2011 to March 2012 at 19 centers in Italy was evaluated. Complications were recorded according to the modified CCS. Results were presented as complication rates per grade. Univariate and binary logistic regression analysis were used for statistical analysis.

Results

Results and limitations: 467 patients were enrolled. Median age was 70 years (range 35–89). UD consisted in orthotopic neobladder in 112 patients, ileal conduit in 217 patients and cutaneous ureterostomy in 138 patients. 415 complications were observed in 302 patients and were classified as Clavien type I (109 patients) or II (220 patients); Clavien type IIIa (45 patients), IIIb (22 patients); IV (11 patients) and V (8 patients). Patients with cutaneous ureterostomy presented a lower rate (8%) of CCS type ≥IIIa ($p = 0.03$). A longer operative time was an independent risk factor of CCS ≥III (OR: 1.005; CI: 1.002–1.007 per minute; $p = 0.0001$).

Conclusions

In our study, RC is associated with a significant morbidity (65%) and a reduced mortality (1.7%) when compared to previous experiences. The modified CCS represents an easily applicable tool to classify the complications of RC and UD in a more objective and detailed way.

Keywords

Bladder cancer; Cystectomy; Urinary diversion; Complications; Clavien

Introduction

Bladder cancer represents the 7th most common cancer in men and the 17th in women.1 and 2 Since the early 1960s, radical cystectomy and pelvic lymphadenectomy have been considered the standard management of muscle invasive bladder cancer (MIBC) and a valid option for selected patients with high grade non muscle invasive bladder cancer (NMIBC).3, 4, 5 and 6 Notwithstanding improvements in surgical technique, technology and preoperative care have reduced the perioperative complication rate and even lowered the perioperative mortality rate from nearly 20% to less than 2%; radical cystectomy (RC) is still associated with a significant perioperative and long term morbidity ranging from 19% to 64% according to the different series.7 However, complications associated with RC have been frequently classified as minor or major based on different definitions, which made an effective comparison of the different series impossible and highlight the fact that standardized methods for reporting data on surgical complications or morbidity after RC are urgently needed.7 The Clavien classification system (CCS) for surgical complications was originally developed in the 1990s and thereafter modified and validated6 and 7; nowadays it will probably represent the upcoming standard for both reporting complications and quality standard.8, 9 and 10 Few retrospective studies, mostly in tertiary referral centers with a long enrollment period and focusing exclusively on ileal urinary diversions, examined complications using a CCS and have reported rates between 48% and 74%.11, 12 and 13

The aim of our study was to prospectively evaluate, in a one-year multicenter Italian cohort of patients, the applicability of the modified CCS in grading perioperative complications of RC and urinary diversions (UDs) in patients with bladder urothelial carcinoma.

Materials and methods

Patients and samples

A consecutive series of patients treated with open RC, lymphadenectomy and UD from April 2011 to March 2012 at 19 centers in Italy were evaluated for complications occurring up to the end of the third postoperative month. The indications for surgery included muscle invasive urothelial carcinoma, selected patients with high grade NMIBC, BCG resistant carcinoma in situ and NMIBC that cannot be managed with transurethral resection. No exclusion criteria were considered. Age, sex, co-morbidities, smoking history, anthropometric parameters including body mass index (BMI), American Society of Anaesthesiologists (ASA) score, history of previous medical and surgical treatments and details of surgery were recorded from all patients. Clinical and pathological stages were evaluated for all the patients according to the TNM 2010 staging system.14 Antiaggregants and anticoagulant drugs were stopped at least 1 week before the operation. Daily administration of subcutaneous low-molecular weight heparin was initiated 12 h before surgery and maintained for at least 4 weeks postoperatively. Polyethylene glycol solution was routinely administered the afternoon before surgery for bowel preparation. An elastic compressive stocking was used as mechanical prophylaxis for deep vein thrombosis (DVT) and third-generation cephalosporin was administered intravenously when anesthesia was initiated and maintained for 5 days postoperatively.

Surgical technique

All operations were performed by an expert qualified uro-oncology consultant in each center.

RC was performed according to the procedure suggested by the International Consultation on Bladder Cancer.15 Lymph node dissection extension included the removal of all lymphatic tissues around the common iliac, external iliac, internal iliac arteries and from the obturator region bilaterally and the presacral region.15 and 16 UD consisted of cutaneous ureterostomy according to the Glenn technique17 and 18; ileal conduit according to the Bricker or Wallace technique11 and 19 and ileal orthotopic neobladder according to the Studer or Camey or Padua techniques.16, 19 and 20

All uretero-intestinal and uretero-cutaneous anastomosis were stented intraoperatively regardless of the form of UDs for at least 12 days. Patients with orthotopic neobladders underwent a contrast cystogram 3 weeks postoperatively and the urethral catheter was removed provided no significant leakage was observed.

Complications evaluation

All complications within 90 days of surgery were prospectively recorded and classified according to the modified CCS8 which stratifies perioperative complications into five grades and focuses mainly on the therapeutic consequences of a complication, emphasizing the level of intervention required to managed it.21 Likewise, perioperative mortality was defined as death from any cause within 90 days of surgery.

Statistical analysis

Statistical analysis was performed using the S-PSS 12.0 software (Chicago, USA). Differences between groups of patients in medians for quantitative variables and differences in distributions for categorical variables were tested with the Kruskal Wallis one way analysis of variance and chi-square test, respectively. Using multiple logistic regression with the enter method, the significant statistical variables as assessed in the univariate analysis were entered and investigated as predictors of severe complications (CCS ≥III) vs. no or low-grade (CCS ≤II) complications. The variables considered for entry into the model included age, sex (categorical), presence of hydronephrosis (categorical), ASA score (categorical variable), operative time, pathological stage (categorical) and type of urinary diversion (categorical). An alpha value of 5% was considered as the threshold for significance. Data are presented as median (range). Odds ratios and 95% CI's were calculated for the parameters in each group using no and low grade complications as a reference group.

Results

Patient characteristics

467 patients were prospectively and consecutively enrolled. Descriptive data of the cohort are summarized in Table 1.

Table 1.

Descriptive preoperative data of 467 patients undergoing radical cystectomy.

Age (yrs) 70 (35–89)

Gender Male: 379 patients

Female: 88 patients

Smoker 246 patients

Anticoagulant treatment 140 patients

Diabetes mellitus 88 patients

Hypertension 278 patients

Ischemic heart disease 93 patients

BMI (kg/m2) 25 (18–46)

Hemoglobin level (g/dl) 13 (9–17)

Chronic renal insufficiency (GFR < 59 ml/min) 35 patients

Hydronephrosis (%) 98 patients

ASA score

I 49 patients

II 195 patients

III 195 patients

IV 28 patients

Tumor size (cm) 4 (1–12)

Tumor lesions (number#) 1 (1–15)

*Data as median (range).

None of the patients received neoadjuvant chemotherapy. All patients underwent RC and lymph nodes dissection. UD consisted in orthotopic neobladder in 113 patients, ileal conduit in 217 patients and bilateral cutaneous ureterostomy in 138 patients. Median operative time was 270 min (95–720); median estimated blood loss was 1290 cc (500–2000); median time to fluid intake was 5 days (2–28). Median time to stool passage was 6 days (3–28). Median length of stay was 13 (6–119) days. Pathological stage was T0 in 28 patients; T1 in 36 patients (4 G1; 7G2 and 25 G3); T2 in 103 patients (44 G2 and 59 G3); T3 in 165 (35.5%) patients (55 G2 and 110 G3); T4 in 99 patients (38 G2 and 61 G3) and CIS in 36 patients (7.8%). Overall 141 patients presented a pathological N stage ≥1.

Clavien classification system evaluation

A total of 415 complications were recorded in 302 patients with an incidence of perioperative complications of 65% (Table 2). Most complications were classified as Clavien type I (109 complications) or II (220 complications). Higher grade complications were observed: 45 Clavien type IIIa, 22 Clavien type IIIb, 11 Clavien type IV and 8 Clavien type V. Overall, 8 patients died and out of them three during the first postoperative month.

Table 2.

Complications of radical cystectomy classified according to the modified Clavien system.

Clavien classification	Complications
Grade 1	109
Ileus paralytic	25
Infections	31
Transient elevation of creatinine	16
Metabolic imbalance	10
Transient reduction of Hb	12
Lymph discharge	6
Transitory ischemic attack	3
Dyspnea	6
Grade 2	220

Blood transfusions 182

Infections 20

Small bowel obstruction 17

Deep venous trombosis 1

Grade 3a 45

Urinary leakage 16

Wound or pelvic Infections 8

Hydronephrosis 5

Small bowel obstruction 8

Lymphocele 3

Pneumotorax 2

Pelvic hematoma 3

Grade 3b 22

Urinary leakage 6

Wound infections 6

Small bowel obstruction or leakage 9

Pelvic hematoma 1

Grade 4a 9

Myocardial infarction 4

Lung failure 4

Kidney failure 1

Grade 4b 2

Urosepsis 2

Grade 58

Overall 415

Overall, 182 patients required blood transfusion for perioperative bleeding. Most of the complications (311 complications) occurred during the initial hospitalization, and the remaining 104 following discharge. No significant association between clinical, pathological variables and the occurrence of any type of complications was observed (Table 3).

Table 3.

Analysis of the complications classified according to the CCS and perioperative patient's characteristics.

	No complications	Complications	p
Patients	165	302	
Age (yrs)	71 (65–76)	70 (35–89)	0.588
Female 23	64	0.054	
BMI (kg/m2)	25.5 (23–34)	25 (22–46)	0.616
Hemoglobin level (g/dl)	13 (9–17)	12 (9–16)	0.254
Hydronephrosis	28	70	0.07
Diabetes mellitus	26	62	0.218
Hypertension	98	180	0.521
Ischemic heart disease	34	59	0.73
Chronic renal failure	27	8	0.075
ASA score			
I	15	34	0.232
II	79	116	
III	65	130	
IV	6	22	
Tumor size (cm)	4 (1–12)	4 (1–10)	0.347
2010 TNM pathological T stage			
T1 or less	17	47	0.442
T2	45	58	
T3–T4	92	172	
CIS	11	25	
2010 TNM pathological N0	114	212	0.441
Operative time (min)	256 (95–640)	272 (95–720)	0.189
Length of stay (days)	12 (6–40)	14 (6–119)	0.534

Data presented as median (range).

Patients with ureterocutaneostomy presented a higher rate of co-morbidity (hypertension, ischemic heart diseases, chronic renal failure), hydronephrosis and as a consequence a higher ASA score when compared to the ileal conduit or to the orthotopic neobladder (Table 4). Advanced disease (pT3-4) was also more frequent in patients who received a cutaneous ureterostomy (Table 4). Ileal conduit and orthotopic neobladder required a significantly longer operative time when compared to cutaneous ureterostomy (p = 0.001).

Table 4.

Patient's characteristics according to the different type of urinary diversions.

	Ureterocutanesostomy	Ileal conduit	Orthotopic neobladder	p
Patients	138	217	113	
Age (yrs)	75.5 (35–89)	71 (47–86)	63 (36–77)	0.001
BMI (kg/m2)	24.6 (23–28)	26.4 (22–46)	25 (27–40)	0.237
Preoperative hemoglobin level (g/dl)	11.6 (9–13)	12.7 (9–17)	13.2 (10–17)	0.008
Hydronephrosis (%)	42	42	14	0.002
Diabetes mellitus	29	42	17	0.485
Hypertension	100	129	49	0.001
Ischemic heart disease	40	41	12	0.001
Chronic renal failure	20	12	3	0.001
ASA score				0.001
I	9	23	17	
II	46	89	60	
III	67	95	33	
IV	16	10	2	
Tumor size (cm)	5 (1–10)	4 (1–12)	4 (1–7)	0.191
2010 TNM path. T stage				0.008
T1 or less	14	34	16	
T2	32	39	32	

T3–T4	88	126	50	
CIS	4	18	14	
2010 TNM path. N0	84	152	80	0.064
Operative time (min)	189 (95–600)	300 (95–720)	290 (105–720)	0.001
Estimated blood loss (cc)	1340 (500–2000)	1600 (500–1713)	1140 (1100/1365)	0.644
Length of stay (days)	12 (6–119)	13 (6–60)	14 (6–35)	0.036

Data presented as median (range).

No significant differences (p = 0.991) were observed for the overall rate of complications in the three different UDs (112 complications in 138 patients for cutaneous ureterostomy; 201 complications in 217 patients for the ileal conduit and 102 complications in 112 patients for the orthotopic neobladder).

High grade (CCS ≥IIIa) complications evaluation

Overall, 65 patients experienced high grade CCS (≥IIIa) complications and 67 reinterventions (general or local anesthesia) were required: 14 for wound or pelvic infections; 22 for urinary anastomosis leakage; 17 for ileal perforation or occlusion; 5 for hydronephrosis; 4 for hematoma, 2 for pneumotorax and 3 for lymphocele. In patients with CCS ≥IIIa a longer operative time and length of stay were observed when compared to patients with no or low grade (CCS ≤II) complications (Table 5). Patients who received a cutaneous ureterostomy presented a significantly (p = 0.03) lower rate of high grade CCS ≥ 3 (11 complications in 138 patients) when compared to ileal conduit (35 complications in 217 patients) and orthotopic neobladder (19 complications in 112 patients). On multivariate analysis, a longer operative time was confirmed to be a significantly independent risk factor of high grade (CCS ≥IIIa) complications (OR: 1.005; CI: 1.002–1.007 per minute; p = 0.0001), despite the type of UD.

Table 5.

Patient's characteristics according to the different grade of complications.

	No complications or CCS ≤II	CCS ≥IIIa	p
Patients	402	65	
Age (yrs)	71 (35–85)	70.3 (10); 70 (43–89)	0.279
Female/male ratio	77	10	0.297
BMI (kg/m2)	25 (22–40)	24 (18–46)	0.724

Hemoglobin level (g/dl)	12.2 (9–17)	13 (9–16)	0.639		
Hydronephrosis (%)	86	12	0.362		
Diabetes mellitus	70	18	0.06		
Hypertension	233	45	0.102		
Ischemic heart disease	80	13	0.550		
Chronic renal failure	27	8	0.096		
ASA score		0.259			
I	40	9			
II	173	22			
III	163	32			
IV	26	2			
Tumor size (cm)	4 (1–12)	4.5 (1–10)	0.697		
2010 TNM pathological T stage			0.761		
T1 or less	55	9			
T2	87	16			
T3–T4	227	37			
CIS	33	3			
2010 TNM pathological N0	121	20	0.559		
Operative time (min)	260 (95–640)	343 (108–720)	0.001		
Length of stay (days)	12 (6–50)	20 (6–119)	0.001		

*Data presented as median (range).

Discussion

Radical cystectomy morbidity and mortality rate

Radical cystectomy and pelvic lymphadenectomy is the standard treatment for patients with muscle invasive or high risk NMIBC although it is associated with a high risk of severe complications.11 and 22 In our prospective multicenter group of patients enrolled for one year and treated with RC and three different types of UD, we observed a low one month (0.63%) and three months (1.7%) mortality rate associated with an elevated (65%) morbidity which was higher when compared to the data reported by Novara et al.11 and

by Shabsigh et al.12 However, our group of patients were older (median 70 years vs. 65 and 68 respectively) and with a higher prevalence of co-morbidities as diabetes or arterial hypertension. Furthermore, they11 and 12 retrospectively evaluated only patients treated in a single tertiary referral, enrolled over a long range of time (5–10 years) using exclusively an ileal UD (ileal conduit, continent pouch or orthotopic neobladder).11 and 12 Our experience included patients from 19 different teaching and non-teaching hospitals and better reflects the real life activity in Italy. In particular, cutaneous ureterostomy was the selected UD in about 25% of our patients. Although cutaneous ureterostomy is performed worldwide in about 2/10% of patients treated with RC,23 it is still a common procedure in Italy and in a real life setting it could be indicated in patients with advanced bladder cancer and higher co-morbidities as observed in our series. In this group of patients we particularly observed, together with advanced bladder cancer, a higher incidence of hydronephrosis and co-morbidities when compared to patients receiving an ileal UD (Table 4). Most of these procedures were performed without any curative intent or to improve patients' survival but only as a palliative procedure to avoid future worsening of the patients' quality of life that may derive from hematuria with clot formation, urinary retention, pain from infiltration of the pelvic nerves and renal failure.

The most common complication categories were hematological (198 complications), gastrointestinal (57 complications), infectious (51 complications), wound related (16 complications) and genito-urinary (30 complications). Although 415 complications were observed in 302 patients, most of them (329 complications) were considered not severe (CCS ≤II) according to the CCS. In this group of patients the most common complication was blood transfusion which was necessary in 182 patients during the perioperative observation time with an average estimated blood loss of 1200 ml which is in the same range reported by other groups (560–3000 ml).24 and 25 The non significant differences in terms of estimated blood loss were observed among the three different UDs which underline how this type of complication can be attributable to the RC procedure independently from the UD procedure.

Radical cystectomy and high grade (CCS ≥IIIa) complications

In our analysis, a small number of patients (65 patients) experienced high grade complications (CCS ≥3a) and most of them were related to small bowel obstruction (17 complications) or anastomosis urinary leakage and hydronephrosis (27 complications). We confirmed in our series how CCS ≥IIIa complications are mostly related to the UD procedure and particularly to the ileal resection and anastomosis or to the ureteric and urethra anastomosis. The relation of CCS ≥IIIa complications with ileal UD can also explain the similar trend of the high rate of these complications observed in all the studies on robotic, open or laparoscopic RC where the ileal UD is always performed through a midline incision11, 21, 25 and 26 independently from the open, laparoscopic or robotic approach.

Furthermore, this hypothesis is confirmed in our series by the group of patients with cutaneous ureterostomy where we observed a lower rate (8%) of CCS ≥IIIa complications when compared to the ileal conduit (16%) and the ileal orthotopic neobladder (17%). Although we acknowledge that ileal conduit and orthotopic neobladder should be considered as the standard UD in patients treated with RC, in our

experience, in patients with significant co-morbidities, cutaneous ureterostomy could be proposed and discussed in selected patients in order to reduce the morbidity associated with ileal UD.

Multivariate analysis showed that operative time was a statistically significant independent predictor of CCS ≥IIIa despite the type of UD. Although our results could be in relation to the reduced statistical power associated with the smaller number of patients who experienced CCS ≥IIIa complications (65 patients), it could reflect that a longer operative time is required in patients with technically demanding procedures in relation to the patient's habit, tumor stage, previous surgery, or intraoperative complications; it can also reflect particular anesthesiological needs and can induce metabolic imbalance, resulting in a higher rate of high grade postoperative complications. The average length of stay after a RC ranges between 7 and 34 days according to the different centers, with significant differences between Europe (longer length of stay) and American (shorter length of stay) hospitals.11 and 12 In our experience the median length of stay was 13 days (range 6–119) and it was significantly longer in patients with high grade complications. However, compared to other series our median length of stay was shorter probably in relation to the different types of UDs included in our series. In particular, patients with cutaneous ureterostomy presented significant shorter hospitals stay when compared to ileal UDs.

Study limitations

Despite the fact that to our knowledge this study represents the largest multi-institution analysis of RC and UDs using the CCS, we must acknowledge some limitations. The relationship between hospital volume and RC outcome in terms of morbidity and mortality is well established.21 In our series 19 different centers from teaching and non-teaching hospitals were involved in this project and the results obtained in our experience could not be referred or transferable to high volume cancer centers. Even though some authors21 took into consideration 50 procedures per year as the desirable cystectomy rate in order to minimize the possible complications, the International Consultation on Bladder cancer has recently proposed an annual rate of 10 RC procedures per hospital as an adequate rate.15 In our series, all the centers involved reached this standard (median 21 RC per center, range 13–40). Another possible limitation of our study is related to the small sample size when compared to other larger American series.12 and 21 However, we decided to reduce the enrollment period to one year and consequently the sample size in order to have a precise and real life picture of these procedures and to minimize the possible influence of the surgical and technological progress which has been particularly evident year after year in the last decades. Finally, although ileal conduit and orthotopic neobladder are considered the standard UDs23 in our series, about 25% of the patients received a cutaneous ureterostomy which influenced our results and reduced the possibility of comparing our entire group of patients with the available evidence. However, we present a real life experience in our study where this type of UD is still a frequent option. Furthermore, including the patients in our series, we better highlighted and demonstrated the direct relationship between high grade complications and ileal UD.

Conclusions

In our study we confirmed, in one year of a real life cohort of patients, that the CCS is a feasible method to evaluate early morbidity after RC and UDs. Although most of the complications were minor, 12% of the patients experienced high grade complications and most of them were observed in patients who received ileal UDs (orthotopic neobladder or ileal conduit). Although mortality rate has dropped significantly over the last decades, perioperative complications remain common.

Acknowledgment statement

The authors acknowledge Kimberlee Manzi from the University “La Tuscia”, Viterbo, Italy, who provided English editing support.

Conflict of interest statement

All authors declare no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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