

Original Article

Retrospective complications assessment of en bloc resection of bladder tumors with the modified clavier classification system

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Abstract: Objectives: To assess peri-operative complications with the Modified Clavier Classification System (MCCS), evaluate the feasibility and safety, and explore predictive indexes for peri-operative complications in transurethral en bloc resection of bladder tumors (ERBT) procedure for non-muscle-invasive bladder cancer (NMIBC). Materials and methods: We retrospectively collected data of 162 consecutive patients who received ERBT for NMIBC from July 2014 to June 2016. All peri-operative complications occurred within 30 days were graded according to MCCS. Logistic regression analysis was used to investigate the impact of each of the factors on the incidence of peri-operative complications. Results: Thirty-nine complications were seen in 33 (20.3%) patients. The most common complication was bleeding related in 21 patients (63.64%). Four (2.47%) patients experienced extra-peritoneal bladder perforation and 3 of them received conservative treatment. Grade I and II complications constituted the majority (90.91%) while grade III was quite uncommon (only 9.09%). Multivariate analysis showed that the operative time, ASA score (≥ 3) and multiple resection sites were independent predictors of peri-operative complications. Conclusions: MCCS can be considered a practical and standardized tool in evaluating peri-operative complications in patients undergoing ERBT. Our results also confirmed that ERBT is a feasible and safe procedure for NIBC with a low complications rate regardless of the energy source. Multiple resection sites, ASA score ≥ 3 and longer operative time can be used as independent predictors for peri-operative complications.

Keywords: Bladder tumors, transurethral resection, en bloc resection, modified clavier classification system, complication

Introduction

Previous studies have suggested that transurethral en bloc resection of bladder tumors (ERBT) might have changed the concept of endoscopic surgery in the diagnosis and treatment of non-muscle-invasive bladder cancer (NMIBC) since ERBT was first introduced in 1997 [1, 2]. Various research groups have already explored the safety and reliability of both laser-based and plasma-based approaches for en bloc resection of bladder tumors [3, 4]. According to a series of studies, conventional transurethral resection of the bladder tumor (cTURBT) is associated with various significant postoperative complication rates ranging from 5.1% to 43.4%

[5]. Due to improvements in surgical technique, endoscope and peri-operative care, peri-operative and intraoperative morbidity of ERBT are lower compared to cTURBT [6]. However, we still lack a systemic complications report that is easy for interpretation of surgical quality assessment. The modified Clavier classification system (MCCS) (Table 1) for surgical complications was originally developed and validated in the 1990s and thereafter modified [5, 7]. It represents the reporting standard for surgical complications and quality assessment [8, 9]. Although some reports graded complications of cTURBT using MCCS [5], no study has yet classified complications of ERBT with MCCS. The aim of our study was thus to know the grade of

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Table 1. Classification of surgical complications according to the MCCS (modified Clavien classification system)

Grade 1	Any deviation from the normal post-operative course without the need for pharmacologic treatment or surgical, endoscopic and radiologic interventions. Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade 2	Complications requiring pharmacologic treatment with drugs other than such allowed for grade 1 complications. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Complications requiring surgical, endoscopic or radiologic intervention.
Grade 3a	Intervention not under general anesthesia.
Grade 3b	Intervention under general anesthesia.
Grade 4	Life-threatening complications (including central nervous system complications) requiring intensive care unit stay.
Grade 4a	Single organ dysfunction (including dialysis).
Grade 4b	Multi-organ dysfunction.
Grade 5	Death of the patient.

Table 2. Descriptive peri-operative data of 162 patients undergoing ERBT

Gender (M)	133 (82.1%)
Age (years)	67.2±10.6
Smoker	105 (64.8%)
BMI (kg/m ²)	26.4±2.88
Diabetes Mellitus	30 (18.5%)
Hypertension	68 (42%)
Anemia	36 (22.22%)
HoL-ERBT group	71 (43.8%)
T stage (WHO 2002)	
Ta	94 (58%)
T1	68 (42%)
Mean resected tumor number	1.59±0.84
Mean maximal tumor size (cm)	2.63±0.91
ASA	
I-II	108 (66.67%)
III-IV	54 (33.33%)

BMI: body mass index; ASA: American Society of Anesthesiologist score.

peri-operative complications of ERBT with MCCS in NMIBC patients.

Materials and methods

Patient characteristics

A retrospective study was carried out at the First Affiliated Hospital of Kunming Medical University, the Second Affiliated Hospital of Kunming Medical University and the Third People's Hospital of Kunming with patients undergoing ERBT for non-muscle invasive bladder cancer (NMIBC) from July 2014 to June 2016 with or without intra-vesical therapy. This study was conducted in agreement with the

guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of the 3 above hospitals. Approximately 226 consecutive cases were identified. Cases without follow-up data (n=29), not suitable for en bloc resection (n=11), or presentation of invasive bladder cancer (n=24) were excluded from the analysis. Data related to patients, tumor and complications which occurred within the 1st month postoperatively were extracted in 162 eligible patients. Bipo-ERBT and HoL-ERBT were all performed by 2 experienced surgeons.

Surgical procedure

En bloc resection of bladder tumors was performed for patients with primary or recurrent bladder tumor. Since tumor size and location were the limiting factors for en bloc resection, single tumor size >4 cm or tumors located at anterior wall or the top of bladder were ruled out. Surgical procedures were performed according to the basic principle described in previous classic reports [10, 11] and care was taken to achieve R0 resections. HoL-ERBT was performed with 550-µm fiber and the following parameter settings: energy 1.5 J, pulse 20 Hz, and resultant power 30 W. Bipo-ERBT was performed with a plasma electrode loop and the following parameter settings: cutting power at 160 W and coagulation power at 80 W. Intra-operative Adjuvant instillation therapy was performed according to the European Association of Urology recommendations [12].

Complications evaluation

All data related to complications within 30 days after surgery were extracted and graded using

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Table 3. Classified complications according to MCCS (modified Clavien classification system)

Grade	Complications	No. Patients	% Incidence
Grade 1	Transient hematuria	17	10.5
	Acute urinary retention	5	3.1
Grade 2	Hematuria requiring blood transfusion	2	1.2
	Medical Complications	6	3.7
Grade 3a	Percutaneous hypogastric drainage	1	0.6
Grade 3b	Active hematuria requiring endoscopic intervention	2	1.2
Overall		33	20.3

Table 4. Peri-operative characteristics of patients with or without complications

	No complications	Complications (CCS \geq 1)	<i>p</i>
Total	129 (79.6%)	33 (20.4%)	
Male	106 (82.18%)	27 (81.82%)	0.96
Age (years)	67.2 \pm 9.6	70.8 \pm 8.7	0.04
Smoker	80 (62.02%)	25 (75.76%)	0.14
BMI (kg/m ²)	25.5 \pm 3.1	26.1 \pm 2.95	0.42
Diabetes Mellitus	25 (19.38%)	5 (15.15%)	0.58
Hypertension	56 (43.41%)	12 (36.36%)	0.46
Anemia	24 (18.6%)	12 (36.36%)	0.03
HoL-ERBT Group	57 (44.19%)	14 (42.42%)	0.73
Bipo-ERBT Group	72 (55.81%)	19 (57.58%)	
T stage (WHO 2002)			0.80
Ta	75 (58.14%)	19 (57.58%)	
T1	43 (33.33%)	10 (30.3%)	
\geq 2 tumors	39 (30.23%)	18 (54.55%)	0.01
Maximal tumor size (cm)	2.64 \pm 0.90	2.57 \pm 0.93	0.69
ASA score			<0.01
I-II	93 (72.1%)	15 (45.45%)	
III-IV	36 (27.9)	18 (54.54%)	
Resection time (min)	28.8 \pm 8.3	36.4 \pm 9.7	<0.01
Postoperative hospital stay (days)	2.7 \pm 1.0	3.6 \pm 1.0	<0.01

BMI: body mass index; ASA: American Society of Anesthesiologist score.

the MCCS adjusted for transurethral procedure [5]. Transient hematuria is defined as hematuria persisted for more than 48 hours and then resolved spontaneously as previously described [13]. Medical complications include bladder irritation, cardiac arrhythmia, urinary tract infection, pneumonia and DVT (deep vein thrombosis). In the final analysis, if 1 patient had more than 1 complication, only the most severe complication was analyzed.

Statistical analysis

Continuous data are reported by mean \pm standard deviation (SD) or median and interquartile

range (IQR) according to their distribution and compared by Student *t* test. Categorical variables are given using frequencies and proportions analyzed by Chi-square test or Mann-Whitney U test. All prognostic factors with a *p* value of <0.25 in univariate analysis were submitted for multiple logistic regression with the method to investigate predictors of complications. The best combined model to predict postoperative morbidity was performed by ROC (receiver operating characteristic) curve. All statistical tests were analyzed using SPSS (SPSS Inc., Chicago, IL, USA, Version 19.0). An alpha value of 0.05 was considered as the threshold for significance.

Results

A total of 162 patients were enrolled in this study, the demographic and tumor characteristics were list in **Table 2**. Mean resection time was 30.4 \pm 8.9 min., Mean hospitalization time was 2.9 \pm 1.1 days. Thirty-three patients (20.3%) were recorded with at least 1 postoperative complications. Among these complications (listed in detail in **Table 3**), 22 were classified as Grade I, 8 as Grade II. Five of these patients had a second combined complication, of which 4 were classified as grade I and 1 as grade II. Percutaneous hypogastric drainage was done in 1 case due to extra-peritoneal bladder perforation (Grade IIIa). Endoscopic intervention was performed in 2 patients with active hematuria (Grade IIIb). Extra-peritoneal bladder perforation were recorded in 4 patients:

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Table 5. Multivariate analysis of possible factors on postoperative complications

Variable	B (SE)	OR (95% CI)	P value
Age	0.046 (0.034)	1.050 (0.98-1.13)	0.17
Multiple/Single Tumor	3.105 (1.135)	1.69 (1.01-4.43)	<0.01*
Smoker (yes/no)	0.017 (0.512)	1.05 (0.39-2.82)	0.92
Anemia (yes/no)	0.614 (0.515)	1.49 (0.62-4.62)	0.39
ASA (III-IV/I-II)	1.021 (0.475)	2.80 (1.12-7.05)	0.03
Resection time	0.264 (0.068)	1.11 (1.06-1.17)	<0.01*

ASA: American Society of Anesthesiologist score. *indicates $p < 0.05$.

open surgery was performed for 1 patient; no additional treatment for other 3 patients with small perforation (≤ 1 cm) except for placing a catheter for about 3-7 days. Obturator nerve reflex (ONR) was completely avoided in HoL-ERBT group, while 5 patients suffered ONR in Bipo-ERBT group, accompanied by resultant bladder perforation in 2 patients. No ERBT-related deaths were noted.

Patients with physical status classification III-IV of American Society of Anesthesiologist score (ASA), older, anemia, multiple tumors (≥ 2) with multiple resection sites, longer operative time were more prone to experience complications, thus experienced longer post-operative hospitalization as expected. No difference in terms of overall complications was noted between HoL-ERBT and Bipo-ERBT group (**Table 4**).

Multivariate analysis was performed to evaluate the impact of possible factors on postoperative complications: only multiple tumors (OR 1.69), longer resection time (OR 1.11), and the ASA III-IV (OR 2.80) were independent predictors of postoperative complications morbidity (**Table 5**). The area of the predictive model combined resection time, the ASA scores and tumor multiplicity under the ROC curve (95% CI) for the prediction of complications were 0.72 (0.63-0.81), achieving a sensitivity of 59.8% and a specificity of 72.66% for predicting postoperative complications (**Table 6**).

Discussion

Most of the cases with transitional cell carcinoma of the bladder present with non-muscle-invasive bladder cancer (NMIBC) at the first diagnosis (70%) [14], transurethral resection of the bladder tumor (TURBT) remains the standard technique for both diagnosis and treat-

ment of bladder tumors [15]. However, the first debate is the “piece-by-piece” technique (the process of gradual exfoliating of tumors) of TURBT can generate a high amount of scattering of cancer cells which may lead to further seeding and implantation. The second problem is that the microanatomy of the tumors was destroyed which made histologic interpretation difficult due to cautery and crushing of the specimens. All publications of the past

years suggests that those shortcomings may be reduced by en bloc resection of bladder tumors [16]. Although complications associated with ERBT are rare, we still lacked an organized assessment study based on a systemic tool such as MCCS to analyze postoperative complications. Considering that several studies had applied MCCS in grading postoperative complications of transurethral resection of bladder tumor, we retrospectively analyzed a cohort of 162 patients who underwent ERBT with bipolar or holmium laser to provide a systematic assessment of postoperative complication with the MCCS. The risk factors for post-ERBT complications were then identified. In our study, all the procedures were performed by 2 senior urologists with uniform similar techniques, thus the postoperative complications are comparable.

The major concern for intraoperative complications was bladder perforation (BP). Several previously published studies have proved that bladder perforation induced by the obturator nerve reflex (ONR) due to electrical stimulation during cTURBT could be avoided by applying laser energy [4, 17]. Only one BP was reported by 4 studies of ERBT by using laser devices [4, 18-20]. In our study, while no ONR was observed in laser group, the incidence rates of BP between the Bipo-ERBT group and the HoL-ERBT group were not obvious, which means surgical techniques rather than energy source come first.

Of all 33 early postoperative complications of ERBT, 90.91% (30/33) were low grade. 63.64% (21/33) were from bleeding associated complications, 2 cases (1.2%) underwent blood transfusion, and another 2 cases (1.2%) received endoscopic intervention. Present research articles on ERBT with information about acute bl-

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Table 6. ROC curve for the prediction of postoperative complications

	Area under the curve	Sensitivity	Specificity
Combination of ASA scores, resection time, and tumor multiplicity	0.72 (0.63-0.81)	59.8%	72.66%

eding are rare, in the series of Kramer et al. 3.2% (7/221) of patients required prolonged bladder irrigation or endoscopic intervention due to acute bleeding [3]. While several groups favored laser ERBT with respect to hemostatic issues compared with cTURBT [3, 17, 20], the energy source was not a risk factor in our study with regard to postoperative bleeding. Only characteristics of the tumor mattered in regard to bleeding. In other words, patients with multiple tumors (≥ 2) had a higher incidence of bleeding.

Laser technique seemed superior with regard to postoperative bladder irritation, which was reported by various authors ranging from 38% to 47.5% [21]. However, bladder catheterization was performed for all patients after the surgery which may cause confusion between catheter-related bladder discomfort (CRBD) and surgery related bladder irritation (SRBD), and both of them shared similar symptoms mimic OAB (overactive bladder) [22]. In our study, 3 patients received Tolterodine to relieve the symptoms, no significant difference was observed between Bipo-ERBT group and HoL-ERBT group in the incidence rate of bladder irritation.

Several publications have shown a correlation between ASA score and postoperative complications in TURBT [23, 24]. In our study, multivariate analysis showed that the operative time, ASA score (≥ 3) and multiple tumors were the independent predictors of postoperative complications. Multiple resection sites and intraoperative complications may also prolong the operative time. ASA scores above 2 were found more commonly in the complication group. The best predictive model combined the ASA scores, resection time, and tumor multiplicity to achieve a sensitivity of 59.8% and a specificity of 72.66%, which could aid the surgeon in predicting postoperative complications.

The limitations of this study are the retrospective study design and small sample size compared to other previous larger series evaluating complications in 2821 patients treated

with cTURBT [25]. In this study, the follow-up was limited to 30-days, urethral strictures and bladder retraction that developed after the follow up were not taken into account, and a single tumor >4 cm or tumors located at anterior or top wall of bladder was ruled out, thus limiting the applicability of our results. Finally, the feasibility of the predictive model still needs further validation. We will try to enrolled more cases with a prospective study design and longer follow-up in the future to verify the results of this study.

Conclusions

Our study proves that ERBT is a safe and reliable procedure with a low complications rate regardless of the energy source. MCCS can be used to grade complications following ERBT, also as a standardized tool for comparisons between different types of endoscopic procedures for bladder tumors. Postoperative complications in ERBT could be avoided by improvement of basic surgical technique. We also suggest that patients with multiple resection sites, ASA score ≥ 3 , and longer operative time may have higher incidence of postoperative complications.

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Disclosure of conflict of interest

None.

Abbreviations

NMIBC, non-muscle-invasive bladder cancer; MCCS, modified Clavien classification system; ERBT, En bloc resection of bladder tumors; TURBT, transurethral resection of the bladder tumor; cTURBT, conventional transurethral resection of the bladder tumor; ONR, obturator nerve reflex; ASA, American Society of Anesthesiologist; CRBD, catheter-related bladder dis-

comfort; SRBD, surgery related bladder irritation; OAB, overactive bladder; BMI, body mass index.

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