

Robot Assisted Radical Cystectomy Outcomes in Micropapillary and Plasmacytoid Variants

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Purpose: To compare the patients who underwent robot assisted radical cystectomy (RARC) and extended pelvic lymph node dissection (EPLND) and whose pathology result was reported as micropapillary variant (MV), plasmacytoid variant (PV) and pure urothelial carcinoma (PUC).

Materials and Methods: The data of 133 patients who underwent RARC and EPLND with the postoperative pathology results reported as MV, PV and PUC were analyzed. According to the postoperative pathology results, patients were divided into two groups in initial analyses as variant pathologies group (n=14) and PUC group (n=119). In secondary analyses, patients were divided into three groups as MV group (n=7), PV group (n=7) and PUC group (n=119). The operative data, oncologic outcomes and complications were compared between the groups.

Results: Median operation time and estimated blood loss were significantly increased in variant pathologies group ($P < 0.001$ and $P = .001$, respectively). The postoperative pathological T stage, positive surgical margin rate and lymph node involvement were also significantly increased in variant pathologies ($P = .001$, $P = 0.004$, $P < 0.001$, respectively). Kaplan-Meier analysis revealed significant decrease in OS and CSS times in PV group compared to PUC group ($P = .048$ and $P = .016$, respectively).

Conclusion: MV and PV are rarely seen variant pathologies with higher pathological T stages. RARC is a minimally invasive surgical technique that can be performed successfully by an experienced surgical team with low morbidity rates and similar oncological results, even in challenging cases.

Keywords: cystectomy; micropapillary urothelial carcinoma; plasmacytoid; robotic surgical procedures; urinary bladder neoplasms

INTRODUCTION

Urothelial carcinoma is the most common malignancy of the bladder, accounting for approximately 90% of bladder neoplasms⁽¹⁾. Approximately 75 % of bladder cancers are classified as pure urothelial carcinoma (PUC), while 25% consist of other histological variants^(2,3). Plasmacytoid variant (PV) and micropapillary variant (MV) are histologically rarely seen subtypes of urothelial cancer of the bladder. They exhibit lymphovascular invasion, high pathological stage and aggressive behavior compared to other urothelial cancers⁽⁴⁾. Through the all types of bladder cancer, the prevalence of PV and MV was reported as 1% and 0.6-2 %, respectively⁽⁵⁻⁸⁾. Due to the rareness of these two variant pathologies, their optimal treatment is controversial⁽⁹⁾. On the other hand, gold standard treatment for muscle-invasive and high-risk bladder cancer is open radical cystectomy (RC) and urinary diversion. Robot-assisted radical cystectomy (RARC) has been used

increasingly worldwide in recent years⁽¹⁰⁾. Robotic surgery has some advantages compared to open surgery as lesser estimated blood loss (EBL), decreased flatus time, decreased need for analgesics and lesser mean hospital stay time with similar oncologic outcomes⁽¹¹⁻¹³⁾. To date, there have been reports on micropapillary and plasmacytoid variants, however, all of the reported RC series were open surgeries and the data regarding to the operation have not been presented. In this current study, we aimed to compare the perioperative, clinical and oncological outcomes of patients who underwent RARC and extended pelvic lymph node dissection (EPLND) and whose pathology result was reported as MV, PV and PUC.

MATERIALS AND METHODS

A quality assurance database of our institution was reviewed and the data of 224 patients who underwent RARC between May 2009 and February 2020 was ana-

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Table 1. Demographic features, clinical characteristics and perioperative data of the patients.

Variables	Variant Pathologies (n=14)	PUC (n=119)	P-value	MV (n=7)	PV (n=7)	PUC (n=119)	P-value
Age at radical cystectomy (years) median (IQR)	60.5 (55.25-67)	63 (56-70)	.292	67 (59-67)	60 (49-61)	63 (56-70)	.299
Gender n (%)			.317			.606	
Male	14 (100)	111 (93.3)	7 (100)	7 (100)	111 (93.3)		
Female	0 (0)	8 (6.7)	0 (0)	0 (0)	8 (6.7)		
BMI (kg/m ²) median (IQR)	26.5 (25.87-27.25)	26 (25.61-26.3)	.212	27 (26-28)	26 (25.48-27)	26 (25.61-26.3)	.417
ASA score n (%)			.125		.13		
I	10 (71.4)	55 (46.2)	6 (85.7)	4 (51.7)	55 (46.2)		
II	2 (14.3)	50 (42)	1 (14.3)	1 (14.3)	50 (42)		
III	2 (14.3)	4 (11.8)	0 (0)	2 (28.6)	4 (11.8)		
IV	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
Smoking history			.022*				
Smoking status n (%)	14 (100)	87 (73.1%)	7 (100%)	7 (100%)	87 (73.1%)		.89
Package /years median (IQR)	30 (20-36)	40 (25-40)	.769	30 (20-30)	30 (20-45)	40 (25-40)	.73
Creatinine level (mg/dL) median (IQR)	1 (0.88-1.12)	1 (0.86-1.2)	.971	1 (0.95-1.2)	1 (0.7-1.1)	1 (0.86-1.2)	.999
Previous intravesical BCG therapy n (%)	2 (14.3)	21 (17.6)	.753	2 (28.6)	0 (0)	21 (17.6)	.351
Diversion type n (%)			.001*				.001*
Ileal loop	11 (78.6)	40 (38.3)	7 (100)	4 (57.1)	40 (38.3)		
Studer pouch	3 (21.4)	79 (61.7)	0 (0)	3 (42.9)	79 (61.7)		
Diversion technique n (%)			.064				.132
Intracorporeal	110 (71.4)	107 (89.9)	5 (71.4)	5 (71.4)	107 (89.9)		
Extracorporeal	4 (28.6)	12 (10.1)	2 (28.6)	5 (71.4)	12 (10.1)		
Neoadjuvant chemotherapy n (%)	2 (14.3)	21 (17.6)	.753	0 (0)	2 (27.6)	21 (17.6)	.351
Adjuvant chemotherapy n (%)	12 (85.7)	31 (26.1)	< 0.001*	7 (100)	5 (71.4)	31 (26.1)	< 0.001*
Median operation time (minute) median (IQR)	360 (335-440)	280 (240-330)	< 0.001*	340 (320-360)	440 (350-440)	280 (240-330)	< 0.001*
EBL (mL) median (IQR)	480 (287-562)	200 (100-300)	.001*	500 (400-540)	300 (200-700)	200 (100-300)	.002*
Blood transfusion n (%)	3 (21.4)	14 (11.8)	.306	1 (14.3)	2 (28.6)	14 (11.8)	.403
Flatus time (days) median (IQR)	3 (3-3)	3 (3-3)	.355	3 (3-3)	3 (3-3)	3 (3-3)	.520
Lodge drain removal time(days) median (IQR)	8 (6-11)	9 (7-11)	.618	7 (6-10)	11 (7-12)	9 (7-11)	.250
Length of hospital stays (days) median (IQR)	12 (10-14)	13 (10-15)	.974	12 (10-14)	13 (9-15)	13 (10-15)	.997

* $p < 0.05$ is considered as statistically significant.

Abbreviations: BMI: Body mass index, ASA: American Society of Anesthesiologists, PUC: Pure urothelial carcinoma, MV: Micropapillary variant, PV: Plasmacytoid variant, EBL: Estimated blood loss, IQR: Interquartile range.

lyzed. Patients whom we performed RARC and EPLND with the postoperative pathology results reported as MV, PV and PUC were included in statistical analysis. All pathologic specimens were re-reviewed by a single genitourinary pathologist (BO). The study was

approved by Ankara Yıldırım Beyazıt University Ethics Committee (11.12.2019 #114).

There were 7 patients with MV, 7 patients with PV and 119 patients with PUC. Patients were divided into groups according to the postoperative pathology re-

Table 2. Preoperative and postoperative pathologic outcomes of the patients.

Variables	Variant Pathologies (n=14)	PUC (n=119)	P-value	MV (n=7)	PV (n=7)	PUC (n=119)	P-value
Pre-cystectomy pathology n (%)			.592				.807
pTa	0 (0)	1.7		0 (0)	0 (0)	1.7	
pT1	1 (7.1)	19 (16)		0 (0)	1 (14.3)	19 (16)	
pT2	13 (92.9)	98 (82.4)		7 (100)	6 (85.7)	98 (82.4)	
Pathological T stage n (%)			.001*				.004*
< pT3	2 (14.3)	72 (60.5)		1 (14.3)	1 (14.3)	72 (60.5)	
≥ pT3	12 (85.7)	47 (39.5)		6 (85.7)	6 (85.7)	47 (39.5)	
LN involvement n (%)			< 0.001*				< 0.001*
pN 0	3 (21.4)	94 (79)		0 (0)	3 (42.9)	94 (79)	
pN (+)	11 (78.6)	25 (21)		7 (100)	4 (57.1)	25 (21)	
Total LNs yield (n) median (IQR)	23 (18-33)	26 (19-33)	.982	30 (21-34)	19 (18-33)	26 (19-33)	.603
PSM n (%)	4 (28.6)	7 (5.9)	.004*	2 (28.6)	2 (28.6)	7 (5.9)	< 0.001*
Incidental prostate carcinoma n (%)	3 (21.4)	33 (27.9)	.616	2 (28.6)	1 (14.3)	33 (27.9)	.897

* $p < 0.05$ is considered as statistically significant.

Abbreviations: PUC: Pure urothelial carcinoma, MV: Micropapillary variant, PV: Plasmacytoid variant, LN: Lymph node, PSM: Positive surgical margin, IQR: Interquartile range.

sults. In initial analyses, patients were divided into two groups in terms of "variant pathologies" including MV, and PV (n=14) and "PUC" (n=119). In secondary analyses, patients were divided into three groups as "MV" (n=7), "PV" (n=7) and "PUC" (n=119). Demographic features and perioperative data of the patients including age, gender, smoking history, body mass index (BMI), American Society of Anesthesiologists (ASA) score, diversion type, EBL, flatus time and length of hospital stay were recorded. The oncologic results were presented including pathologic stages, overall survival (OS) time and cancer specific survival (CSS) time.

Preoperative abdominal computed tomography (CT) or magnetic resonance imaging (MRI) was performed in all patients for local clinical staging. In addition, non-contrast thorax CT, and when necessary, bone scintigraphy and positron emission tomography-CT were performed in all patients to detect distant organ metastasis.

The complications were classified according to Clavien-Dindo classification and complications at 0-90 days were presented. Since the ileal loop or Studer pouch was formed either extracorporeally or intracorporeally, the operation time was defined as the time period during the course of cystectomy and EPLND. Patients who had previous abdominal surgery and radiotherapy (RT) were excluded from the study, since they may adversely affect the operation time due to the intra-abdominal adhesions.

Abdomen CT or MRI and thorax CT were performed at the postoperative 3rd month follow-up. The following controls were performed twice a year through clinical and radiological evaluation.

Statistical analysis

Statistical analysis was carried out by using the SPSS for Windows 17.0 (SPSS Inc. IL, USA) software package. Normality of the data was tested via Shapiro-Wilk test. Mann-Whitney *U* test and Kruskal-Wallis test were used for not normally distributed continuous variables and the data were presented as Median (IQR).

Fisher's exact test was used for categorical variables and the data were presented as n (%). Bonferroni correction was performed in post hoc analyses. Correlation between the cumulative survival times and histopathological subtypes were studied with Kaplan-Meier analysis (Log rank test). With the confidence interval (CI) of 95%, a *P*-value of less than .05 was considered as statistically significant.

RESULTS

Among a total of 224 patients, 91 patients were excluded from the study. Of those 91 patients; 18 patients had previous abdominal surgery, 3 patients received RT due to prostate carcinoma, 64 patients had other variant pathologies and 7 patients had both previous abdominal surgery history, and other variant pathologies. In final analyses, the data of the remaining 133 patients with the diagnosis of MV (n=7), PV (n=7) and PUC (n=119) were analyzed.

Demographic features, clinical characteristics and perioperative data of the patients were presented at **Table 1**. All of the patients with MV and PV were male. Ileal loop formation was significantly increased in variant pathologies compared to PUC group ($P = .001$). Diversion type was significantly different also in three group comparisons ($P = .001$) which was found to be due to the increased ileal loop formation in MV group compared to PUC ($P = .001$), in subgroup analyses. EBL was significantly increased in variant pathologies ($P = .002$). There was also significant difference in terms of EBL in three group comparisons ($P = .001$) and subgroup analyses revealed that the difference was due to the significant increase in MV group compared to PUC ($P = .002$). There was a significant increase in median operation time in variant pathologies ($P < .001$). The difference was also significant in three group comparisons ($P < .001$) which was related with the significant increase in median operation time both in MV group ($P = .009$) and PV group ($P = .001$), compared to PUC. Smoking history was found as significantly higher in

Table 3. Intraoperative and postoperative complication data of the patients according to Clavien-Dindo classification.

Variables	Variant Pathologies (n=14)	PUC (n=119)	P-value	MV (n=7)	PV(n=7)	PUC (n=119)	P-value
Complications (n)							
A. Intraoperative	0	1		0	0	1(3b)	
B. Postoperative							
Grade							
1	1	8		1	0	8	
2	2	8		0	2	8	
3a	0	3		0	0	3	
3b	1	1		1	0	1	
4	1	0		0	1	0	
5							
Minor Complications (Grade 1-2) n (%)	3 (21.4)	46 (38)	.253	1 (14)	2 (28)	46 (38)	.386
Major Complications (Grade 3-5) n (%)	2 (14)	30 (25)	.517	1 (14)	1 (14)	30 (25)	.664
Readmission rate due to minor complication n (%)	3 (21.4)	13 (11)	.376	1 (14)	2 (28)	13 (11)	.371
Readmission rate due to major complication n (%)	2 (14)	14 (12)	.784	1 (14)	1 (14)	14 (12)	.963

* $p < 0.05$ is considered as statistically significant.

Abbreviations: PUC: Pure urothelial carcinoma, MV: Micropapillary variant, PV: Plasmacytoid variant.

variant pathologies compared to PUC ($P = .022$). Two patients (27.6 %) in PV group and 21 patients (17.6 %) in PUC group received neoadjuvant chemotherapy. Adjuvant chemotherapy was given to all patients in MV group (100 %), 5 patients in PV group (71.4 %) and 31 patients in PUC group (26.1 %). There was significant difference between the variant pathologies and PUC groups in terms of receiving adjuvant chemotherapy ($P < .001$). Post hoc analyses revealed that the difference was found to be due to the significant increase in MV subgroup ($P < .001$).

Preoperative and postoperative pathologic outcomes were presented in **Table 2**. The postoperative pathological T stage was presented as $< pT3$ stage and $\geq pT3$ stage. A significant increase in $\geq pT3$ stage was observed in variant pathologies compared to PUC group ($P = .001$). The three group comparison was also revealed significant difference ($P = .004$) which arised from the higher $\geq pT3$ rate both in MV and PV com-

pared to PUC ($P = .014$). LN involvement was significantly increased in variant pathologies compared to PUC ($P < .001$). The difference was also significant in three group analyses ($P < .001$) and was found to be due to the increased LN involvement in MV group ($P < .001$). PSM rate was significantly increased in variant pathologies ($P = .004$). The three group comparison was also revealed significant difference in PSM ($P < .001$), which was due to the increase both in MV and PV compared to PUC ($P < .001$).

The data regarding to intraoperative and postoperative 0-90 day complications were presented in **Table 3**. A patient with PUC necessitated blood transfusion intraoperatively (grade 2) that was the only intraoperative complication in our series. None of the cases required conversion to open surgery.

The median follow-up time was 47 months. In Kaplan-Meier Analysis, median OS time for variant pathologies and PUC was 42.2 and 70.2, respectively,

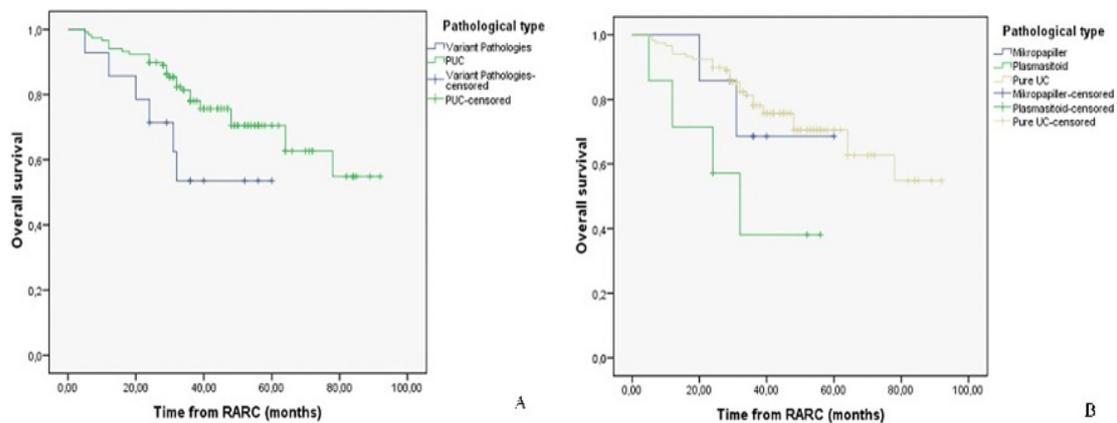


Figure 1. A. Overall survival time for PUC (upper curve) (70.2 months, IQR: 63.8-76.5, n=119) and variant pathologies (lower curve) (44.7 months, IQR: 33.6-55.6, n=14). **B.** Overall survival time for PUC (upper curve) (70.2 months, IQR: 63.8-76.5, n=119), MV (middle curve) (50.1 months, IQR: 36.2-61.7, n=7) and PV (lower curve) (33.2 months, IQR: 18.2-48.3, n=7).

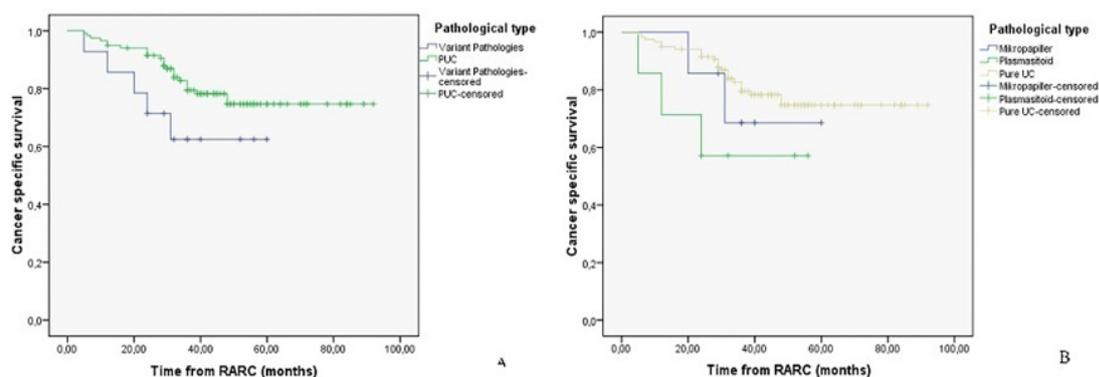


Figure 2.A. Cancer specific survival time for PUC (upper curve) (77.1 months, IQR: 70.3-81, n=119) and variant pathologies (lower curve) (months, IQR: 31.1-53.1, n=14), **B.** Cancer specific survival time for PUC (upper curve) (77.1 months, IQR: 70.3-81, n=119), MV (middle curve) (51.1 months, IQR: 36.2-61.7, n=7) and PV (lower curve) (37.8 months, IQR: 21.8-53.8, n=7).

and similar between the two groups ($P = .064$). The median OS time for MV and PV was 50.1 and 33.2 months, respectively, and significant difference was found in three group comparisons ($P = .048$) which was observed as related with the decreased OS time in PV group compared to PUC, in subgroup analyses ($P = .014$, log rank) (Figure 1). Median CSS time for PUC and variant pathologies was 77.1 and 44.7 months, respectively. In subgroup analyses, median CSS time was observed as 51.1 and 37.8 months in MV and PV, respectively. The CSS time was not significantly different between the variant pathologies and PUC group ($P = .054$). However, the subgroup analyses in three group comparisons revealed a significantly decreased median CSS time in PV group compared to PUC ($P = .016$, log rank) (Figure 2).

DISCUSSION

MV and PV are rarely seen urothelial carcinoma subtypes which are clinically important due to their poorer prognosis, aggressive course and inexplicit optimal treatment approach. Previous studies on these two var-

iant pathologies were all conducted on open surgical series. In addition, the operative data and complication results have not been reported yet in any of the studies conducted to date. To the best of our knowledge, our current study is the first one to present the variant pathology results of a robotic cystectomy series. Our study is also important to provide the operative and complication data of these two rarely seen variant pathologies. In a study including 205 patients, Keck et al. compared 9 MV, 18 PV and 178 PUC cases. All patients received adjuvant chemotherapy and their OS times were reported as 64.2 months in PUC, 27.4 months in PV, and 62.6 months in MV. There is no difference between the three groups in terms of cancer stage⁽¹⁴⁾. However, their results conflict with the current study, as well as the literature, since they found no difference between the groups in terms of lymph node metastasis and pathological T stage⁽¹⁵⁻¹⁹⁾. Sui et al. compared 869 MV and 389,603 PUC cases in a study including patients in all preoperative pathological stages in terms of transurethral resection pathology results. They reported the OS time as 44.7 months for MV. Consistent with the cur-

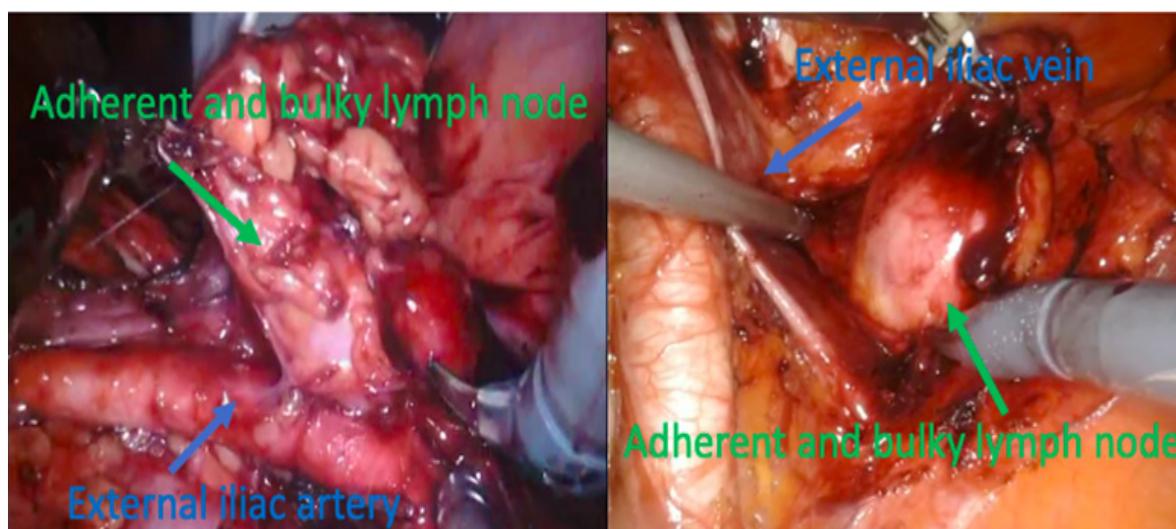


Figure 3. Bulky and adherent lymph nodes which were visualized in variant pathology cases during RARC and EPLND.

rent study they found higher pathological T stage and LN stage in MV. However, they did not present any operative data and they did not specify the OS times through the patients to whom they performed RC (380 MV patients and 40,151 PUC patients)⁽¹⁵⁾. Fairey et al. reported higher pathological stage but similar LN involvement rate in MV cases in their study including totally 1,380 patients who underwent open RC and whose pathology results were reported as PUC in 1,347, and MV in 33 patients. The OS time was not significantly different between MV and PUC cases⁽¹⁶⁾. The current study also revealed similar median OS times through the MV and PUV patients besides a significant increased LN stage in MV compared to PUC.

In a study conducted by Li et al., 1,312 PUC and 98 PV patients were compared. This study was also conspicuous to include the highest number of PV patients, in the literature. They reported higher pathological stage, PSM rate and LN involvement in PV patients. They found median OS time as 3.8 years in PV and 8 years in PUC patients⁽¹⁷⁾. Kaimakliotis et al. reported decreased median OS time and CSS time in PV cases (19 and 22 months, respectively) in a study involving 30 PV and 278 PUC patients. They reported higher LN involvement, LN stage, pathological T stage and PSM rate in PV patients⁽¹⁸⁾. Cockerill et al. compared 46 PV cases with 972 PUC cases and found higher pathological T stage, PSM rate and decreased OS time in PV patients⁽¹⁹⁾. The current study has also consistent results in terms of significantly decreased OS time, as well as CSS time, higher pathological T stage and increased PSM rate in PV patients.

In current study, the mean operation time was longer in both PV and MV cases, compared to PUC. This may be considered as a result of the higher LN involvement and the prolonged LN dissection time due to the technique difficulties related with the bulky and adherent lymph nodes in patients with variant pathologies (**Figure 3**). The increased pathological T stage in variant pathologies which means extravesical dissemination of the tumor may also be considered as another difficulty that may lead to prolonged mean operation time. The significant difference in mean EBL has been interpreted as the consequence of similar mechanisms. However, the increased EBL not absolutely states a significant increase in need for blood transfusion as observed in the current study.

The current study revealed that the major, and the minor complication rates and readmission rates due to the major, and the minor complications were similar between the variant pathologies and PUC, both in initial and secondary analyses. None of the cases necessitated conversion to open surgery. This can be explained by the situation that the operations are performed in a high volume center by an experienced surgical team on robotic procedures.

The current study had some limitations regarding to the single centered design and retrospective nature. Diversion type was significantly different between the three groups related with the increased ileal loop formation in MV group compared to PUC. However, the literature on this specific subject exploring the safety and efficacy of RARC with intracorporeal urinary diversion is very limited. As this was a retrospective study and the number of patients in the variant histology group is limited, it is not easy to draw strict conclusions about

the diversion type. Robotic surgery is a novel procedure compared to open surgery. Therefore, patient series underwent robotic surgery has been covered in a narrower time interval than open surgery. The single centered design and novelty of the technique lead to limitation in number of patients included in this current study in terms of variant pathologies. The long term oncologic results were not presented in the current study, however, our short-term oncological results were found to be compatible with the literature.

CONCLUSIONS

This study has significant results to reveal the operative data, complications and oncologic outcomes of the rarely seen and clinically significant variant pathologies of bladder cancer which underwent RARC. Robotic cystectomy is a minimally invasive surgical technique that can be performed by an experienced surgical team with low morbidity rates and similar oncological results even in challenging cases.

CONFLICT OF INTEREST

All authors declare that, there is no conflict of interest in connection with this paper.

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