

Outcomes of Neoadjuvant Chemotherapy in Patients with Variant Histology after Robot-Assisted Radical Cystectomy: Results from the International Robotic Cystectomy Consortium

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ABSTRACT

Introduction and Objective: We sought to describe the utilization and outcomes of neoadjuvant chemotherapy (NAC) among patients with variant histology who underwent robot-assisted radical cystectomy (RARC).

Methods: A retrospective review of the multi-institutional prospectively maintained International Robotic Cystectomy Consortium (IRCC) database was performed (4139 patients from 33 institutions in 12 countries). Patients with preoperative variant histology (whether pure variant or mixed with urothelial) were identified and then grouped based on receipt of NAC. Descriptive statistics were used to summarize the data. Kaplan Meier method was used to depict recurrence-free (RFS), disease-specific (DSS), and overall survival (OS). Multivariate Cox regression models were used to depict variables associated with RFS, DSS, and OS.

Results: 278 patients had preoperative variant histology and 23% of these received NAC. Variant histology was absent in 43% of patients at RARC. There was no significant difference in terms of pT, pN, positive margins or recurrence rates between those who received NAC and those who did not ($p > 0.05$ for all). Patients who received NAC had RFS of 84% and 76% at 1 and 3 years, respectively, compared to 74% and 59% for those who did not receive NAC, respectively (log rank $p = 0.12$). Patients who received NAC had DSS of 85% and 81% at 1 and 3 years, respectively, compared to 89% and 72% for those who did not receive NAC, respectively (log rank $p = 0.96$). Patients who received NAC had OS of 77% and 65% at 1 and 3 years, compared to 76% and 60% for those who did not receive NAC, respectively (log rank $p = 0.70$). pN+ (HR 2.29, 95% CI 1.383.78, $p = 0.01$) and pT3/T4 (HR 4.68, 95% CI 2.508.76, $p < 0.01$) were associated with worse RFS. pN+ (HR 2.76, 95% CI 1.395.44, $p < 0.01$) and pT3/T4 (HR 4.10, 95% CI 1.839.17, $p = 0.01$) were associated with worse DSS. pN+ (HR: 2.58, 95% CI: 1.6 4.14, $p < 0.01$) and pT3/T4 (HR 3.03, 95% CI 1.745.28, $p < 0.01$) were associated with worse OS. Positive margins (HR 2.17, 95% CI 1.25 3.77, $p < 0.01$) and higher Charlson Comorbidity Index (HR 1.25, 95% CI 1.091.43, $p < 0.01$) were associated with worse OS.

Conclusion: Twenty-three percent of patients with preoperative variant histology received NAC. Of these, 43% had no variant histology after cystectomy. There was no significant difference in oncologic outcomes between patients with variant histology who received NAC and those who did not.

Keywords: bladder cancer, variant histology, neoadjuvant chemotherapy, urothelial carcinoma, robot-assisted, cystectomy, survival.

JMS: 2023; 26(3):10-17 DOI: <https://doi.org/10.33883/jms.v26i3.1295>

INTRODUCTION

Radical cystectomy and pelvic lymph node dissection remain the mainstay of treatment for muscle-invasive bladder cancer and refractory non-muscle invasive disease¹⁻³. Neoadjuvant chemotherapy has been associated with improved survival, especially for patients with predominant urothelial histology⁴. The presence of variant histology has

been traditionally considered an adverse feature, and aggressive management is usually advised even for non-

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Access this article online



Website:
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DOI:
<https://doi.org/10.33883/jms.v26i3.1295>

How to cite this article: Ahmad A, Shah A, Jing Z, Doherty P, Wagner A, Kaouk J, Stöckle M, Kim E, Dasgupta P, Khan M, Balbay D, Aboumohamed A, Roupert M, Maatman T, Rha K, Richstone L, Wiklund P, Hussein A, Guru K. Outcomes of Neoadjuvant Chemotherapy in Patients with Variant Histology After Robot-Assisted Radical Cystectomy. JMS 2023; 26 (3)10-17

Received: 2023-08-25 Accepted: 2023-09-27



muscle invasive disease^{6,7}. The role of neoadjuvant chemotherapy in the setting of variant histology remains controversial⁹. The low incidence of variant histology, concerns about complete response and delay of surgical management have limited the utilization of NAC among this cohort¹⁰.

In this context, we sought to describe the utilization of NAC among patients with preoperative variant histology, and further investigate its effect on perioperative outcomes and survival by utilizing a multi-institutional prospectively maintained database, the International Robotic Cystectomy Consortium (IRCC).

METHODS

A retrospective review of the IRCC database was performed (4139 patients from 33 institutions in 12 countries). Patients with variant histology (whether pure or mixed with urothelial) before robot-assisted radical cystectomy (RARC) were identified. Patients were then divided into those who received NAC and those who did not. Data was analyzed for demographics (age, race, sex, Body Mass Index (BMI), Charlson Comorbidity Index (CCI), and American Society of Anesthesiologists® (ASA) scores), preoperative variables (presence of variant histology, prior radiation therapy, previous abdominal surgery, hydronephrosis, and clinical TNM staging), perioperative details (operative time, transfusion, blood loss, lymph node yield, diversion type and approach, duration of inpatient and ICU stay, and cystectomy era), and postoperative characteristics (change in histology, surgical margins, high tumor grade, pathologic TNM staging, recurrences, complications, and mortality).

Descriptive statistics were used to summarize the data utilizing Pearson Chi-square and Fischer Exact tests for categorical data, and Wilcoxon rank test for continuous variables. Kaplan Meier method was used to depict recurrence-free (RFS), disease-specific (DSS), and overall survival (OS). Multivariate Cox regression models were used to depict variables associated with RFS, DSS, and OS. All analyses were performed using SAS 9.4 software. All tests were double-sided with statistical significance set at $p < 0.05$.

RESULTS

278 patients with preoperative variant histology were

included in the study (squamous differentiation-33%, micropapillary-24%, adenocarcinoma-9%, sarcomatoid-9%, and small cell carcinoma-6%) (Table 1). Twenty-three percent received NAC. Those who received NAC were younger (64 vs. 69 years, $p=0.003$), had higher BMI (29 vs. 27 kg/m², $p=0.01$), had prior abdominal surgery less frequently (43% vs. 60%, $p=0.02$), had higher cN+ (14% vs. 4%, $p=0.03$), and shorter inpatient stay (6 vs. 7 days, $p<0.01$) (Table 2). Postoperatively, 43% of these patients did not show variant histology in the final specimen (Table 1).

Table 1: Preoperative and postoperative histological variants

Variant Histology Subtype	Preoperative, n (%)	Postoperative, n (%)
Adenocarcinoma	26 (9)	14 (5)
Lymphoepithelial	1 (0.4)	0 (0)
Micropapillary	68 (24)	30 (11)
Nested	13 (5)	6 (2)
Neuroendocrine	5 (2)	4 (1)
Plasmacytoid	15 (5)	18 (6)
Sarcomatoid	25 (9)	19 (7)
Signet Cell	6 (2)	5 (2)
Small Cell	17 (6)	11 (4)
Squamous	93 (33)	45 (16)
Pure Urothelial	--	120 (43)

Patients who received NAC had RFS of 84% and 76% at 1 and 3 years, respectively, compared to 74% and 59% for those who did not receive NAC, respectively (log rank $p=0.12$). Patients who received NAC had DSS of 85% and 81% at 1 and 3 years, respectively, compared to 89% and 72% for those who did not receive NAC, respectively (log rank $p=0.96$). Patients who received NAC had OS of 77% and 65% at 1 and 3 years, compared to 76% and 60% for those who did not receive NAC, respectively (log-rank $p=0.79$) (Figure 1a-c).

On the Multivariate analysis, pN+ (HR 2.29, 95% CI 1.38-3.78, $p=0.01$) and pT3/T4 stage (HR 4.68, 95% CI 2.50-8.76, $p<0.01$) were associated with worse RFS. $p<0.01$ (HR 2.76, 95%CI 1.39-5.44, $p=0.01$) and pT3/T4 stage (HR 4.10, 95% CI 1.83-9.17, $p=0.01$) were also associated with worse DSS. Positive margins (HR 2.17, 95% CI 1.25-3.77, $p<0.01$), CCI (HR 1.25, 95% CI 1.09-1.43, $p<0.01$), $p<0.01$ (HR 2.58, 95% CI 1.6-4.14, $p<0.01$), and $p<0.01$ stage (HR 3.03, 95% CI 1.74-5.28, $p<0.01$) were associated with worse OS (Table 3).

Table 2: Perioperative outcomes of patients who underwent RARC for variant histology (NAC vs no NAC)

Patient descriptors	No NAC	NAC	All	p-value
Number of Patients	213 (77)	65 (23)	278	
Age, mean (SD), years	69.31 ± 10.36	64.38 ± 11.15	68.16 ± 10.73	<0.01
Sex: male, n (%)	142 (67)	46 (71)	188 (68)	0.65
Body Mass Index, median (IQR), kg/m ²	27 (24-31)	29 (26-33)	28 (24-32)	0.01
White Race	198 (95)	58 (92)	256 (94)	0.35
High ASA score	129 (61)	42 (66)	171 (62)	0.56
Charlson Comorbidity Index before NAC	5 (4-7)	5 (4-6)	5 (4-7)	<0.01
Prior radiation treatment	25 (12)	5 (8)	30 (11)	0.37
Previous abdominal surgery	123 (60)	28 (43)	151 (56)	0.02
Preoperative N+	8 (4)	8 (14)	16 (7)	0.03
Preoperative Hydronephrosis	38 (19)	16 (25)	54 (20)	0.29
Preoperative Pure Variant Histology	53 (25)	9 (14)	62 (22)	0.06
Preoperative cT3/cT4	21 (10)	12 (19)	33 (12)	0.08
ICU admission after NAC	89 (42)	27 (42)	116 (42)	1.00
ICU stay duration, median (IQR), days	1 (1-2)	2 (1-3)	1 (1-2)	0.23
Inpatient stay duration, median (IQR), days	7 (6-10)	6 (5-8)	7 (5-9)	<0.01
History of blood transfusion	17 (8)	8 (13)	25 (9)	0.32
Number of lymph node yield	20 (14-28)	19 (15-26)	20 (14-28)	0.89
Intracorporeal Urinary Diversion approach	155 (75)	53 (85)	208 (77)	0.09
Neobladder Urinary Diversion	22 (10)	13 (20)	35 (13)	0.05
Estimated blood loss, mL	300 (150-500)	200 (150-300)	250 (150-450)	0.07
Operative time, median (IQR), hours	7 (6-8)	7 (6-8)	7 (6-8)	0.47
Postoperative N+, n (%)	61 (29)	23 (35)	84 (30)	0.36
Postoperative pT3/T4, n (%)	103 (48)	34 (52)	137 (49)	0.67
Positive tumor margin, n (%)	27 (13)	10 (15)	37 (13)	0.54
Return to OR within 30 days, n (%)	9 (4)	3 (5)	12 (4)	1.00
Return to OR within 48 hours, n (%)	2 (1)	1 (2)	3 (1)	0.56
RARC yearly volume, mean (SD)	26.05 ± 14.26	23.43 ± 15.37	25.44 ± 14.54	0.04
Cystectomy Era: before 2010, n (%)	48 (23)	2 (3)	50 (18)	< 0.01
Cystectomy Era: 2011-2015, n (%)	39 (18)	18 (28)	57 (20)	
Cystectomy Era: 2016 and after, n (%)	126 (59)	45 (69)	171 (62)	
Any complications, n (%)	144 (68)	47 (72)	191 (69)	0.54
Complications: 0-30 days, n (%)	108 (51)	35 (54)	143 (51)	0.67
Complications: 0-90 days, n (%)	125 (59)	42 (65)	167 (60)	0.47
High grade complications, n (%)	63 (30)	20 (31)	83 (30)	0.88
High grade complications: 0-30 days, n (%)	36 (17)	9 (14)	45 (16)	0.70
High grade complications: 0-90 days, n (%)	45 (21)	15 (23)	60 (22)	0.73
Any recurrence, n (%)	60 (28)	12 (18)	72 (26)	0.15
Any distal recurrence, n (%)	48 (23)	12 (18)	60 (22)	0.61
Any local recurrence, n (%)	24 (11)	3 (5)	27 (10)	0.15
Number of deaths, n (%)	66 (32)	17 (27)	83 (31)	0.64

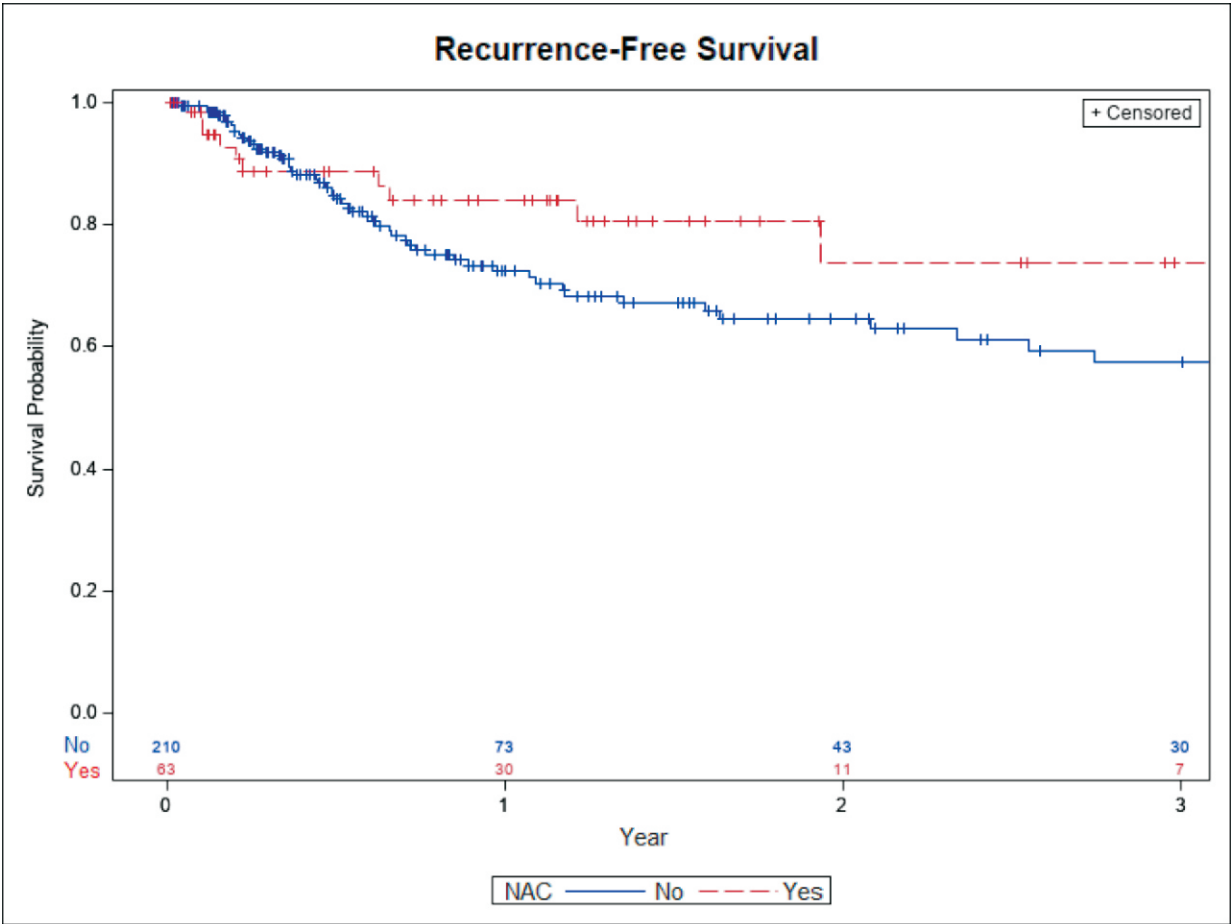
Table 3: Multivariate model depicting variables associated with RFS, DSS and OS

RFS	Hazard Ratio	95% Confidence Interval	p-value
pN+	2.29	1.38 – 3.78	< 0.01
pT3/T4 stage	4.68	2.50 – 8.76	< 0.01
DSS	Hazard Ratio	95% Confidence Interval	p-value
pN+	2.76	1.39 – 5.44	< 0.01
pT3/T4 stage	4.10	1.83 – 9.17	< 0.01
OS	Hazard Ratio	95% Confidence Interval	p-value
Positive margins	2.17	1.25-3.77	< 0.01
Charlson Comorbidity Index	1.25	1.09-1.43	<0.01
pN+	2.58	1.60-4.14	<0.01
pT3/T4	3.03	1.74-5.28	<0.01

Supplementary Table 1: Changes in histology before and after RARC

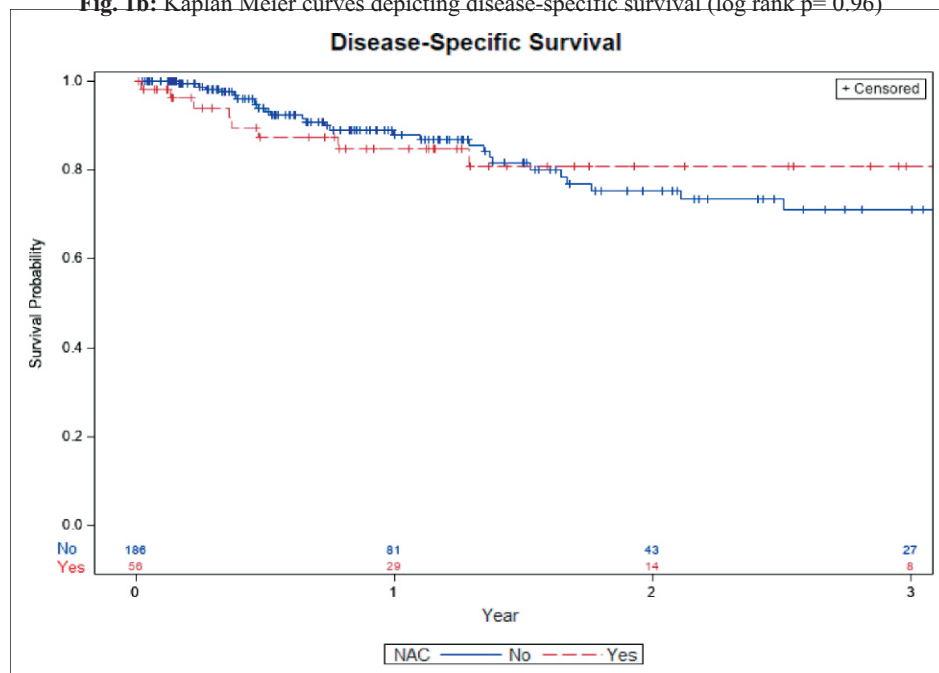
Changes in histology	Frequency, (%)
New variants after RARC	36 (13)
Same variants after RARC	122 (44)
Pure urothelial after RARC	120 (43)

Fig. 1a: Kaplan Meier curves depicting recurrence-free survival (log rank p= 0.12)



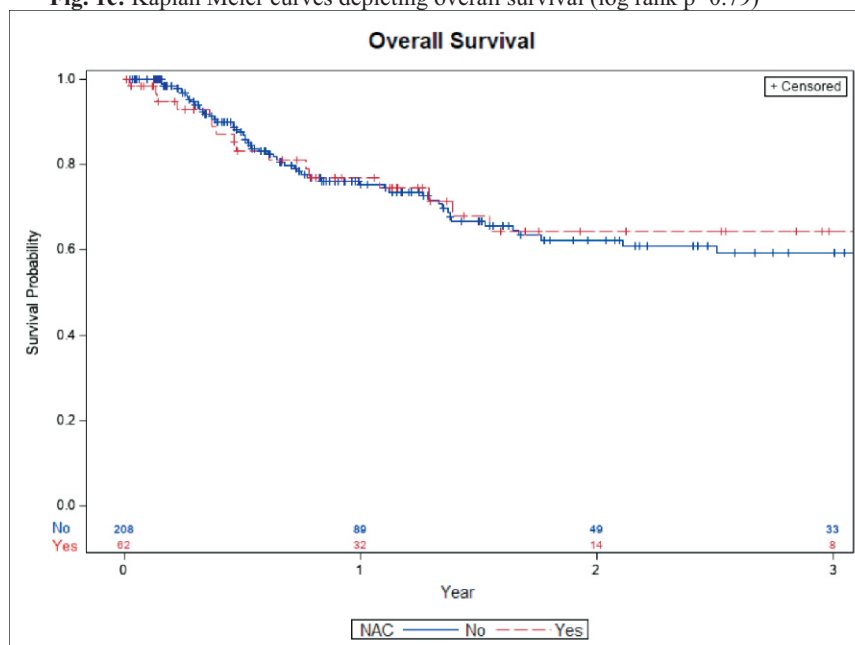
Survival Rate			
Group	Years		
	1	2	3
Preoperative VH, No NAC	0.74	0.66	0.59
Preoperative VH, NAC	0.84	0.76	0.76

Fig. 1b: Kaplan Meier curves depicting disease-specific survival (log rank $p=0.96$)



Survival Rate			
Group	Years		
	1	2	3
Preoperative VH, No NAC	0.89	0.77	0.72
Preoperative VH, NAC	0.85	0.81	0.81

Fig. 1c: Kaplan Meier curves depicting overall survival (log rank $p=0.79$)



Survival Rate			
Group	Years		
	1	2	3
Preoperative VH, No NAC	0.76	0.63	0.60
Preoperative VH, NAC	0.77	0.65	0.65

DISCUSSION

Although level I evidence supports the use of NAC in patients with organ-confined muscle-invasive urothelial carcinoma of the bladder, it remains controversial whether a similar benefit can be achieved in patients with variant histology or not^{13,14}. Currently, there is a lack of sufficient evidence on the ideal treatment strategy for the less common, yet more aggressive, variant histology subtypes of urothelial carcinoma of the bladder (whether urothelial carcinomas with variant histology or purely variant histology)^{9,12}.

The National Comprehensive Cancer Network (NCCN) has made several recommendations for the treatment of specific variant histology. Recommendations include that tumors with urothelial histology inclusive of squamous, adenocarcinoma, micropapillary, nested, plasmacytoid, and sarcomatoid variants should be treated in the same manner as that of urothelial carcinoma. Notably, NAC has not been mentioned to have a proven role in the treatment of pure squamous and pure adenocarcinoma. For cancers having any small cell component or neuroendocrine features with limited stage involvement, four cycles of systemic therapy with cisplatin and etoposide are recommended.

A retrospective analysis of the Indiana University Bladder Cancer Database compared patients with plasmacytoid variant (PCV) with urothelial carcinoma (UC) at the time of cystectomy. Plasmacytoid histology patients were noted to have higher rates of pT3/pT4, nodal involvement, and positive surgical margins compared to the urothelial group. Following NAC, the plasmacytoid group had a higher incidence of postoperative tumor recurrence and they were reported to have lower median OS¹⁸. Li et al. reported that the reason for the worse prognosis associated with PCV was not the nature of the variant histology itself, since there was no statistically significant association between the PCV and OS, but rather due to other associated adverse features such as higher rates of extravesical disease, positive nodal disease and soft tissue positive surgical margins. A study describing the response of PCV to systemic therapy compared patients who underwent initial cystectomy to those who received NAC. It was found that patients who only underwent surgery were more likely to have extravesical spread of disease¹⁹. Another study reported that although patients with the plasmacytoid variant had

comparatively worse pathological features, this was not associated with worse overall mortality²⁰. Our study showed similar findings. There was no statistically significant benefit for NAC in terms of RFS, DSS, or OS. Extravesical disease and nodal status positive margins remain the main determinants of survival.

Studies have shown that response rates for 5-fluorouracil-based chemotherapy in the adenocarcinoma variant have been as high as 48%, and Cetuximab and Sunitinib have also proven to be of some benefit for this variant²¹. In another study, although tumors with adenocarcinoma were more likely to have organ-confined disease, there was no significant improvement in overall survival⁵.

There is mixed data regarding the benefit of NAC for the micropapillary variant. One study found that down-staging to pT0 occurred in 45% after NAC compared to 13% after radical cystectomy only. This down-staging was associated with lower rates of disease recurrence (21% vs 79%) and better OS (92% vs 25%) after two years. However, these results were not statistically significant^{22,23}. In the same vein, another report showed pathologic down-staging to pT0 in 45% of patients with micropapillary bladder cancer who were treated with NAC, suggesting that the use of NAC should not be undermined in cases with variant histology, especially advanced disease, despite the lack of statistically significant survival benefit²³. In another study, the National Cancer Database was used to review cases of micropapillary and urothelial carcinoma from 2004 to 2014. Patients with both types of cancer were treated with radical cystectomy with or without NAC or adjuvant chemotherapy. While patients with UC had an OS of 91.9 months, the OS of patients with MPBC was only 44.7 months ($p < 0.01$)²⁶. A study that reported on 30 cases of nested variant cases with both pure and mixed urothelial forms found that only 13% of patients responded to NAC¹⁶.

In our study, 43% of patients who had initially variant histology before RARC were found to have no variant histology postoperatively. This finding is supported by publications describing discrepancies between clinical and pathologic staging after cystectomy operations³⁰. Since the presence of variant histology has been linked to higher bladder tumor staging, loss of variant histology may be linked to the down-staging of tumors.

Our study is not free of limitations. First, the retrospective study design comes with its limitations. Second, due to the small number of patients with variant histology, we grouped all of them which makes it hard to delineate the effect of NAC for each specific variant. Third, a central pathology review was not performed. IRCC is a multinational and multi-institutional, with variations in treatment and follow-up protocols.

CONCLUSION

Twenty-three percent of patients with preoperative variant histology received NAC. Forty-three percent had no variant histology postoperatively. There was no significant difference in oncologic outcomes between patients who received NAC and those who did not.

Funding : Nil

Conflict of Interest: None

Written informed consent: Taken

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