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Clinical Outcomes of Micropapillary Urothelial Carcinoma of the Bladder Treated With Radical Cystectomy

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Abstract. *Background/Aim: This study examined the treatment outcomes of radical cystectomy (RC) for micropapillary subtype (MPS) bladder cancer treated at our hospital. Patients and Methods: Histopathological findings of RC specimens collected from 2003 to 2020 were evaluated. Recurrence-free survival (RFS) and overall survival (OS) after RC, as well as the efficacy of chemotherapy in cases of recurrence, were retrospectively assessed. Results: Of 202 patients who underwent RC, seven (3.4%) had MPS bladder cancer. All seven patients underwent immediate RC without neoadjuvant chemotherapy. The median patient age was 58 years (range=52-71 years), and all patients were male. After RC, median RFS was 14 months (range=6-115 months), and median OS was 31 months (range=18-115 months). The clinical tumor stage was cT1 or lower in two patients (28.5%), cT2 in two patients (28.5%), and cT3 or higher in three patients (42.8%). No preoperative lymph node metastasis was observed. The pathological tumor stage was pT1 or lower in one patient (14.2%), pT2 in one patient (14.2%), and pT3 or higher in five patients (71.4%). The pathological lymph node stage was observed in five patients (71.4%). Although six of seven patients (85.7%) received adjuvant chemotherapy, all patients experienced relapse. The objective response rates of primary and secondary chemotherapy at relapse were both 33%. One patient received immune checkpoint inhibitor therapy and maintained stable disease for 12 months. Conclusion: The recurrence rate after RC for MPS bladder cancer was high, and prognosis was poor.*

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Bladder cancer is the fourth most common malignancy in men, being responsible for 82,290 new cases and 16,710 deaths in the United States in 2023 (1). Bladder cancer has a variant type in 30% of cases (2), and these variants have a progressive nature and carry a poor prognosis (3, 4). The micropapillary subtype (MPS) of bladder cancer, one of the histological subtypes of urothelial carcinoma, was first reported in 1994. MPS urothelial carcinoma of the bladder is estimated to comprise 0.7% of all bladder cancers, it is often detected at an advanced stage, and generally has a poor prognosis (5). Meanwhile, 40% of cases of MPS bladder cancer involve muscle layer invasion at diagnosis (6). The standard treatment for muscle layer-invasive bladder cancer is radical cystectomy (RC), but because of the aggressive nature of MPS, RC is also recommended for T1 invasive bladder cancer (7). However, because of the rarity of this disease, there are only reports from single centers with small numbers of cases or studies using databases containing limited information. Therefore, this study evaluated the prognosis and outcomes of patients with invasive MPS bladder cancer who underwent RC at our institution.

Patients and Methods

Patient population. This retrospective study enrolled patients who underwent RC for invasive bladder cancer at our hospital between May 2003 and December 2020. A full-time pathologist reviewed the pathology of total bladder specimens for each patient. The classification of histopathologic types was based on the 2022 WHO classification. Invasive urothelial carcinoma with variant histology was defined as the presence of both urothelial carcinoma and other morphologies within the same tumor. The histological type of MPS was identified among the cases of urothelial carcinoma with variant histology. The prognosis after RC and drug therapy was also evaluated. The procedures in this study were approved by the Ethics Committee of the Occupational and Environmental Medicine University of Japan (Kitakyushu, Japan; approval number H28-047).

Evaluation. Postoperative follow-up consisted of physical and clinical examinations and CT, which were performed every six months until the fifth year and every year thereafter. Appropriate additional tests were performed as symptoms appeared. Recurrence was defined as local recurrence in the pelvic region, enlargement of the regional lymph nodes, or distant metastases. Recurrence-free survival (RFS) was calculated from the date of RC to that of the first evidence of clinical recurrence, death from any cause, or the last follow-up if the patient was alive without evidence of recurrence. Overall survival (OS) was calculated from the date of RC to that of death from any cause or the last follow-up if the patient was alive.

Statistical analysis. All statistical analyses were performed using EZR ver. 1.63 (Easy R, Vienna, Austria), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). RFS and OS were estimated using the Kaplan–Meier method.

Results

Between May 2003 and December 2020, 202 patients underwent total bladder resection at the University of Occupational and Environmental Health, and seven of these patients were diagnosed with MPS bladder cancer. Table I presents the background characteristics of patients with the MPS variant. The median age at surgery was 58 years (range=52-71 years), and all patients were male. The preoperative clinical stage was cT1 in two patients (28.5%), cT2 in two patients (28.5%), cT3 in two patients (28.5%), and cT4 in one patient (14.2%).

All patients underwent RC and pelvic lymph node dissection without preoperative adjuvant chemotherapy (AC). Of these patients, the pathological tumor stage was pTa, pT2, pT3, and pT4 in one (14.2%), one (14.2%), four (57.1%), and one patient (14.2%), respectively. Five patients (71.4%) had metastasis in the dissected lymph nodes, and two patients (28.5%) had no metastasis. Postoperative AC was administered in six patients, including gemcitabine and cisplatin (GC) in five patients and methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) in one patient.

Table I. *Patient characteristics*.

Characteristics	Number of patients (%)
Age, median (range)	58 (52-71)
Sex, n (%)	
Male	7 (100)
Female	0 (0)
Clinical tumor stage, n (%)	
≤T1	2 (28.5)
T2	2 (28.5)
≥T3	3 (42.8)
Pathological tumor stage, n (%)	
≤T1	1 (14.2)
T2	1 (14.2)
≥T3	5 (71.4)
Pathological lymph node status, n (%)	
N0	2 (28.5)
N1	1 (14.2)
N2	4 (57.1)
Lymphovascular invasion, n (%)	
Negative	1 (14.2)
Positive	6 (85.7)
Percentage of micropapillary component, n (%)	
≥60%	4 (57.1)
<60%	3 (42.8)
Adjuvant chemotherapy, n (%)	
Not administered	1 (14.2)
GC	5 (71.4)
MVAC	1 (14.2)

GC: Gemcitabine and cisplatin; MVAC: methotrexate, vinblastin, adriamycin and cisplatin.

The chemotherapy regimen at relapse is presented in Table II. The overall response rate (ORR) was 33% for first-line therapy, 33% for second-line therapy, and 0% for third-line therapy. One patient received pembrolizumab, and stable disease (SD) was achieved for 12 months.

The median observation period was 31 months (range=18-116 months). Six patients died of cancer, and one patient survived. Median RFS was 14 months [95% confidence interval (CI)=6-18 months, Figure 1], whereas median OS was 31 months (95%CI=18-67 months, Figure 2). The median extent of MPS rate was 60%. Median OS was 24.5 months (range=18-36 months) for patients with MPS rate ≥60%, *versus* 67 months (range=31-116 months) for those with MPS rate <60%. Two patients with pT2 or less were also admitted. The MPS rate was 10% in patients with pTa lesions, compared with 20% for patients with pT2a lesions. Meanwhile, 60%-95% of MPS cases were pT3 or higher.

Discussion

In this study, we investigated the outcomes of seven patients with MPS bladder cancer (cT1–T4N0M0) without preoperative metastasis. All patients underwent immediate

Table II. *Observed efficacy of pharmacotherapy in patients with micropapillary bladder cancer.*

	Response to chemotherapy			
Regimens	PD	SD	PR	CR
First line (n=6)				
Gemcitabine+Cisplatin	2	0	1	0
Paclitaxel+Gemcitabine	1	0	0	0
Nedaplatin+Paclitaxel	0	0	1	0
Pembrolizumab	0	1	0	0
Second line (n=3)				
MVAC	0	0	1	0
Gemcitabine+Carboplatin	0	1	0	0
Paclitaxel+Gemcitabine	1	0	0	0
Third line (n=2)				
Docetaxel	1	0	0	0
Paclitaxel+Gemcitabine	1	0	0	0

PD: Progression disease; SD: stable disease; PR: partial response; CR: complete response; MVAC: methotrexate, vinblastin, adriamycin and cisplatin.

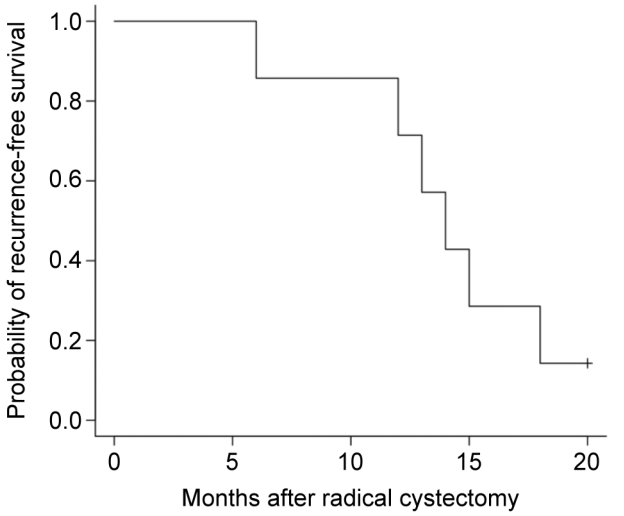

Figure 1. *Recurrence-free survival among seven patients with micropapillary subtype bladder cancer after radical cystectomy.*

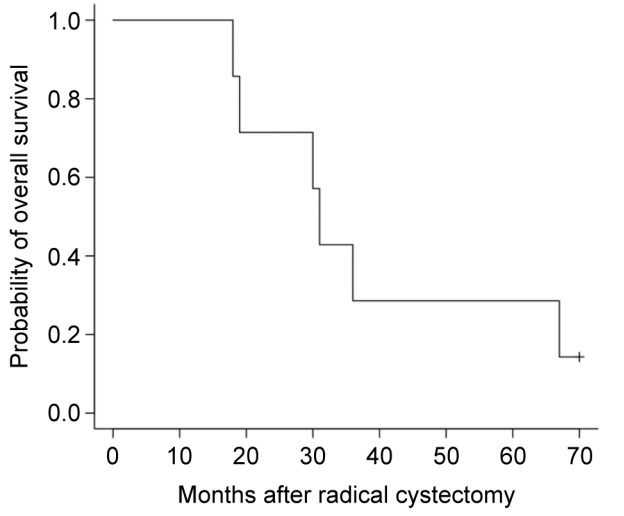

Figure 2. *Overall survival among seven patients with micropapillary subtype bladder cancer after radical cystectomy.*

RC. Despite postoperative AC, the recurrence rate was high. The response rate to systemic chemotherapy after recurrence was also low, and the duration of response was short, indicating a poor prognosis.

MPS, first described by Amin *et al*. (5) in 1994, is a rare subtype of urothelial carcinoma in urinary bladder that accounts for 0.7%-2.2% of all urothelial carcinomas. Regarding upper urinary tract urothelial cancer, squamous differentiation is the most common subtype, but MPS is an extremely uncommon neoplasm (8). MPS bladder cancer is often diagnosed at an advanced stage, and it progresses rapidly thereafter. In 2007, Kamat *et al*. (7) studied bacille Calmette-Guérin intravesical therapy in 27 patients with MPS non-invasive bladder cancer. At a median of 8 months post-treatment, 18 (67%) of the patients with initially non-muscle–invasive disease exhibited disease progression, and six (22%) developed metastatic disease. In addition, the neoadjuvant chemotherapy (NAC) + RC group included a higher percentage of patients with non-organ localized disease (>pT3) than the immediate RC group. Furthermore, the NAC + RC group did not have longer OS than the immediate RC group (7). Based on this evidence, we decided to perform immediate RC.

Some authors reported that the T stage increases, and patient prognosis worsens as the percentage of MPS increases. Alvarado-Cabrero *et al*. compared 76 patients with pure urothelial carcinoma (PUC) and 38 patients with MPS and reported a 2.4-fold increased relative risk of death in patients with a micropapillary component exceeding 50% compared with the PUC group (9). Another report defined the extent of MPS as localized (<10%), moderate (10%-50%), and extensive (>50%) and examined the pathologic stage according to the percentage of MPS. All four patients with extensive MPS had a high pathologic stage of pT3 or pT4. Eighty percent (8/10) of cases of moderate MPS were pT3 or pT4. Meanwhile, 84% (5/6) of cases of localized MPS were pT1 or pTa. From these findings, it was concluded that the infiltrative potential was high at moderate or higher levels (10). Furthermore, it has been reported that the presence of ≥80% variant histology in urothelial carcinoma could be an independent predictor of recurrence and mortality after RC (11).

In a report of 11 patients with MPS, five received four courses of MVAC as AC after RC, all of whom experienced relapse and died (12). Masson-Lecomte *et al*. compared the AC outcomes of 31 patients with MPS and 235 patients with PUC and reported that MPS was associated with higher relapse rates after RC and platinum-based AC than PUC (13). In addition, in a large cohort of 3,963 patients, 23% of whom had variant histology and 18% (723) of whom received AC, AC administration was associated with improved survival outcomes only in patients with PUC, whereas it had no effect on variant histology (14).

In recent years, the favorable effects of NAC on MPS have been recorded in scattered cases. Meeks *et al*. detected pT0 disease in 13 of 29 patients (45%) who underwent NAC with GC (15). In a recent systematic review, NAC was associated with pathologic complete response (ypT0) rates of 11%-55%, but it was not associated with RFS, cancer-specific survival, or OS (6). A study using the National Cancer Database (2004-2017) reported that NAC for MPS resulted in pathologic downstaging to pT1 or less (including pT0, pTa, and pTis) in 34% of patients. However, no improvement in OS was achieved (16). Using the Surveillance, Epidemiology, and End Results database, researchers reported that the effect (pathologic response) of NAC was not different from that of PUC, and NAC for MPS was associated with a non-significant trend toward prolonged OS (17). The VESPER trial, a randomized third-tier trial, revealed that dose-dense MVAC as NAC improved 3-year PFS and 5-year OS compared with the effects of GC. In this trial, MPS responded similarly to NAC as PUC (18).

In the present study, we encountered a patient who received an immune checkpoint inhibitor (ICI) and maintained SD for 12 months. In KEYNOTE-045, a clinical trial of pembrolizumab in urothelial carcinoma, a sub-analysis indicated that pembrolizumab was more effective in variant types of cancer (19). A multicenter retrospective study in Japan reported the efficacy of ICI therapy in metastatic urothelial carcinoma with variant histology in clinical practice. In 81 patients with PUC and 22 patients with urothelial carcinoma with variant histology, ICI treatment led to a superior ORR for urothelial carcinoma with variant histology than PUC, whereas OS was comparable (20). In March 2022, nivolumab, a programmed cell death protein 1 inhibitor, was approved for the treatment of muscle layer-invasive urothelial carcinoma with a high risk of recurrence.

In addition, Minato *et al*. reported that the response rate of systemic chemotherapy for urothelial carcinoma with variant histology was equivalent to that of PUC (21).

Based on the aforementioned findings, future treatment strategies should include aggressive NAC, postoperative adjuvant nivolumab depending on the postoperative pathological findings, and early ICI use at the time of recurrence.

Regarding study limitations, this study was retrospective, and it included a small number of cases. In addition, no women were investigated. Meanwhile, multiple different regimens were used for chemotherapy.

This study provides an assessment of the prognosis of a rare subtype of bladder cancer. Given the rarity of the MPS, these findings could be immediately useful to physicians involved in its diagnosis and treatment. The study investigated a long period of nearly 20 years. The investigation covering this period gave the researchers a greater opportunity to identify potentially relevant cases. The research further illustrates the need to develop new treatment regimens and identify diagnostic markers for this rare disease. These findings could specifically prompt research to determine the efficacy of immune checkpoint inhibitors in combination with radical surgery in this patient population.

Conclusion

The recurrence rate after RC of MPS was high, and the prognosis was poor.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

Kazumasa Jojima: Conceptualization, methodology, investigation, data curation, statical analysis, writing of the original draft. Akinori Minato: Supervision, review, revision of the manuscript. Hirotsugu Noguchi, Yojiro Tsuda: examination of the pathological findings. Naohiro Fujimoto: Supervision. All Authors discussed, verified, and approved the final version of the article.

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