

Case Report

## A Case of Metastatic Urachal Cancer Including a Neuroendocrine Component Treated with Gemcitabine, Cisplatin and Paclitaxel Combination Chemotherapy

Shin Ebara<sup>a\*</sup>, Yasuyuki Kobayashi<sup>a</sup>, Katsumi Sasaki<sup>a</sup>, Motoo Araki<sup>a</sup>,  
Morito Sugimoto<sup>a</sup>, Koichirou Wada<sup>a</sup>, Kei Fujio<sup>a</sup>, Atsushi Takamoto<sup>a</sup>,  
Toyohiko Watanabe<sup>a</sup>, Hiroyuki Yanai<sup>b</sup>, and Yasutomo Nasu<sup>a</sup>

Departments of <sup>a</sup>Urology, and <sup>b</sup>Pathology, Okayama University Graduate School of Medicine,  
Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan

The present case report describes a case of recurrent and advanced urachal carcinoma including neuroendocrine features with iliac bone metastasis after partial cystectomy and adjuvant chemotherapy consisting of irinotecan and cisplatin in a 32-year-old man. He received gemcitabine/cisplatin/paclitaxel (GCP) combination chemotherapy, consisting of gemcitabin (1,000 mg/m<sup>2</sup>) on day 1, 8, cisplatin (70 mg/m<sup>2</sup>) on day 1, and paclitaxel (80 mg/m<sup>2</sup>) on day 1 and 8. After three cycles of chemotherapy, PET-CT showed complete regression of the disease. So the patient underwent total cystourethrectomy, and histological examination showed an almost complete pathological response. External beam radiation therapy was also given to the ileac bone metastasis regions. However, PET-CT taken 17 months after the external beam radiation showed multiple lung metastases. He received GCP chemotherapy again, which resulted in a complete response again after three cycles of chemotherapy. This is the first report on GCP chemotherapy used not only as a salvage chemotherapy but also as a rechallenge regimen for metastatic urachal cancer including a neuroendocrine component.

**Key words:** urachal cancer, neuroendocrine component, gemcitabine, cisplatin, paclitaxel

Urachal cancer is a rare malignancy, and the standard treatment is en bloc resection. The prognosis of recurrent and metastatic urachal cancer is extremely poor, because there is no established chemotherapy regimen. The choice of regimen is largely based on case reports. The present report is the first to describe the use of gemcitabine/cisplatin/paclitaxel (GCP) combination chemotherapy for recurrent and metastasis urachal cancer including a neuro-

endocrine component.

### Case Report

A 32-year-old man presented to a previous hospital complaining of gross hematuria. Cystoscopy, magnetic resonance imaging (MRI) and computed tomography (CT) showed a bladder tumor at the dome of the bladder. He was treated with partial cystectomy, and histological examination showed adenocarcinoma, which

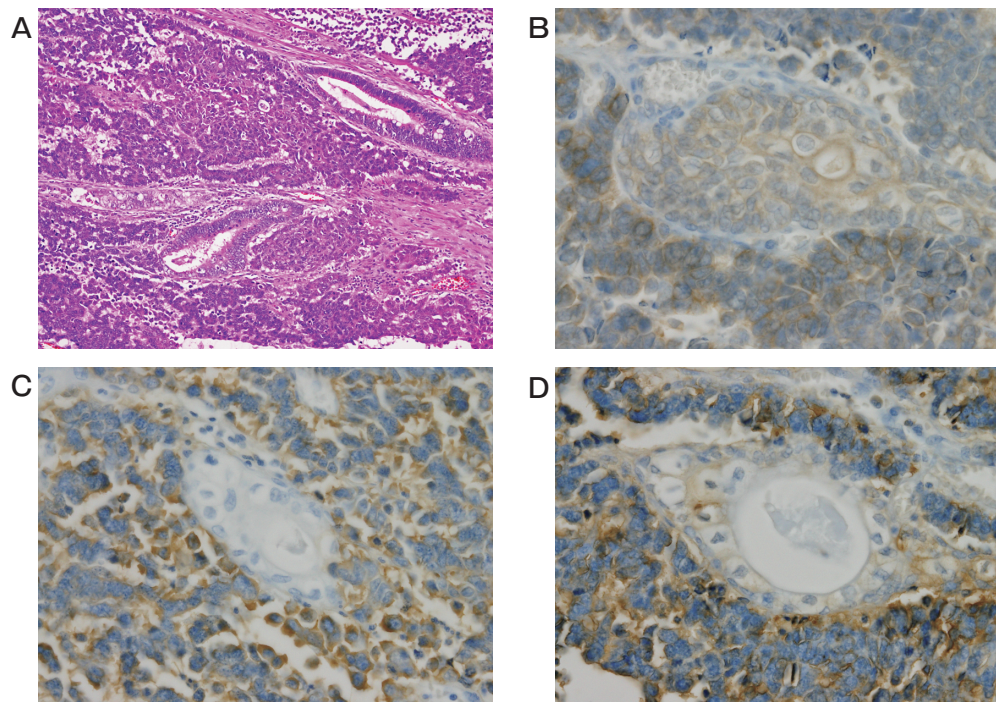
Received August 26, 2015; accepted February 2, 2016.

\*Corresponding author. Phone: +81-86-235-7287; Fax: +81-86-231-3986  
E-mail: [pjcr7j4j@cc.okayama-u.ac.jp](mailto:pjcr7j4j@cc.okayama-u.ac.jp) (S. Ebara)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

spread from the urachus and extended to the bladder muscle and peritoneum. He was diagnosed with urachal adenocarcinoma with peritoneal invasion, then referred to Okayama University Hospital for additional treatment. A second look at the pathologic samples by a pathologist at our university revealed a mixed type of adenocarcinoma and small cell carcinoma using hematoxylin and eosin staining (Fig. 1A), and immunohistological examination revealed a dominant neuroendocrine by CD56 (Fig. 1B), synaptophysin (Fig. 1C) and chromogranin-A staining (Fig. 1D). Three cycles of irinotecan (CPT-11, 70mg/m<sup>2</sup>) on day 1, 15 and cisplatin (CDDP, 80mg/m<sup>2</sup>) on day 1 chemotherapy were introduced according to the chemotherapy regimen for neuroendocrine gastric cancer. One year after the chemotherapy, cystoscopy showed tumor recurrence at the bladder dome (Fig. 2), MRI showed extravesical invasion and ileac bone metastasis, and positron emission tomography (PET-CT) also showed high uptake of 18F-FDG at the bladder dome and ileac bone (Fig. 3). Then, a GCP chemotherapy regimen was administered every 4 weeks and 3 cycles. This regimen consisted of GEM (1,000mg/m<sup>2</sup>) on day

1, 8, CDDP (70mg/m<sup>2</sup>) on day 1, and paclitaxel (PTX, 80mg/m<sup>2</sup>) on day 1, 8. After the 3 cycles of GCP chemotherapy, PET-CT showed complete regression of the bladder and ileac bone disease. Then total cystourethrectomy and pelvic lymphadectomy were performed. Histological examination showed a small volume (less than 1%) of residual viable cells, a major volume of necrosis and fibrosis in the bladder region and no lymph node metastasis. Furthermore, external beam radiation therapy (a total of 50 Gy in 25 fractions) was also given to the ileac bone metastasis regions at 1 month after the operation. However, 17 months after the external beam radiation, PET-CT showed multiple lung metastases (Fig. 4A). Three cycles of GCP chemotherapy were again administered, and PET-CT showed that the lung metastasis had disappeared after chemotherapy (Fig. 4B). The patient remained free of disease at 3 months after treatment. Although grade 3 bone marrow suppression occurred during GCP chemotherapy, the patient completed treatment without interruption or reduction of the chemotherapy dose.



**Fig. 1** The hematoxylin and eosin histology (A) suggested adenocarcinoma and small cell carcinoma. Immunohistological examination by CD56 (B), synaptophysin (C), and chromogranin-A staining (D) suggested dominantly proliferated neuroendocrine components around the adenocarcinoma.

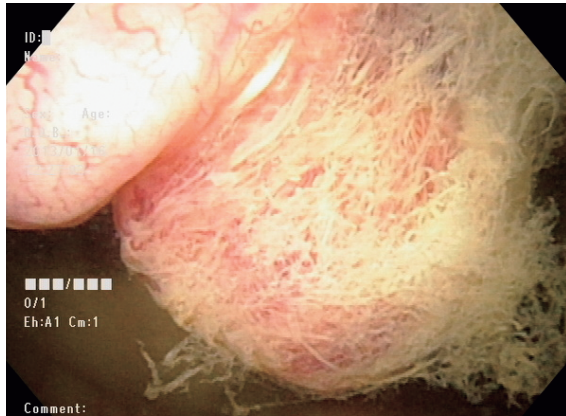


Fig. 2 Cystoscopy showed a non-papillary tumor at bladder posterior wall.

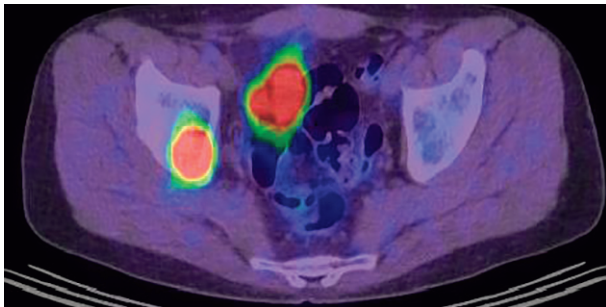


Fig. 3 PET-CT showed a solitary mass at the iliac bone and extravasica (SUV max of 18.62).

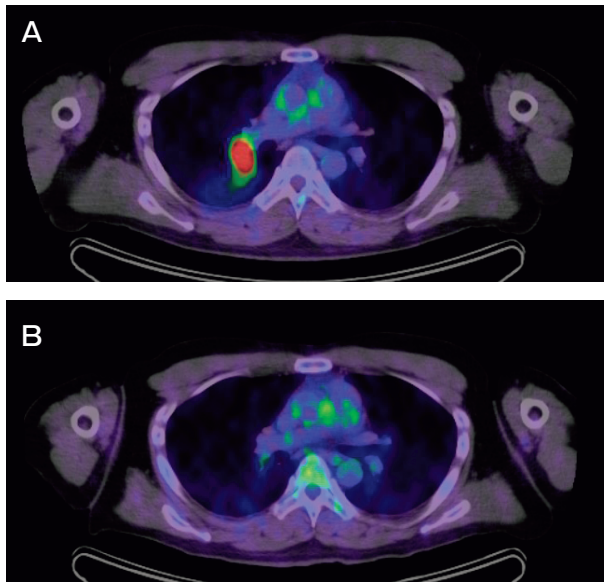


Fig. 4 PET-CT of the lung metastasis. (A) High uptake of 18F-FDG in rt lung (SUV max of 17.67) before GCP chemotherapy. (B) The high uptake disappeared in the lung.

## Discussion

Urachal carcinoma is a rare malignancy of the bladder which accounts for less than 1% of all bladder cancers, and its histological feature is usually adenocarcinoma, although other subtypes have been described [1]. The prognosis of metastatic urachal cancer is extremely poor. Ashley *et al.* reviewed the clinicopathological features and cancer-specific survival of 66 urachal carcinoma patients at their institution and reported that 92% with metastatic urachal carcinoma died of their disease, the median time from the diagnosis of metastasis to death was just over 1 year, and no difference in the time from metastasis to death was noted between patients who did and did not receive chemotherapy [2].

Unlike other cancers, there is currently no standard chemotherapy regimen for the treatment of urachal cancers. According to the National Comprehensive Cancer Network (NCCN) guidelines (version 2; 2015), cystectomy or partial cystectomy with en block resection of the urachal ligament is recommended for local disease, and clinical trial or combination chemotherapy may be considered for selected advanced-disease patients. Histologically, urachal adenocarcinoma has been found to be similar to gastric and colon adenocarcinoma, and in some studies CPT-11-based chemotherapy [3] and FOLFOX-based chemotherapy [4] have been reported to be efficacious for treating metastatic urachal adenocarcinoma. On the other hand, for small cell carcinoma or neuroendocrine component of bladder cancer, neoadjuvant chemotherapy and local treatment including cystectomy are recommended, and the suggested primary chemotherapy regimens are similar to those recommended for small cell lung cancer in the NCCN guidelines.

The treatment course of our case is shown in Table 1. The pathological examination of the first partial cystectomy revealed a dominant neuroendocrine component (not adenocarcinoma) and peritoneal invasion of cancer cells. This neuroendocrine component in urachal cancer is very rare and made it difficult to decide on whether to administer an adjuvant treatment. Although there is no evidence the efficacy of adjuvant chemotherapy, we focused on the pathological finding of peritoneal invasion and decided to introduce adjuvant chemotherapy. Some reports have shown the

Table 1 Treatment course of this case report

Duration from previous therapy	Evaluation before therapy		Therapy	Evaluation after therapy	
	Cystoscopy / Imaging			Pathology	Imaging
	Tumor at bladder dome No metastasis		Partial cystectomy	Adenocarcinoma/ Neuroendocrine (Fig. 1)	
			CPT-11 / CDDP 3C		
12 months	Bladder recurrence (Fig. 2) Ileac bone metastasis(Fig. 3)		GCP 3C	CR	
			Total cystourethrectomy Pelvic lymphadectomy	Almost CR	
			RT for ileac bone metastasis		
17 months	Lung meta. (Fig. 4A)		GCP 3C	CR (Fig. 4B)	

efficacy of CPT-11 plus CDDP chemotherapy for small cell lung cancer [5] and gastric small cell carcinoma [6]; therefore, we undertook a gastric small cell carcinoma regimen in our hospital. However, local recurrence and distant metastasis were observed at one year after the CPT-11 plus CDDP chemotherapy.

At this time, salvage chemotherapy was discussed. We focused on GEM/CDDP chemotherapy, which has been reported to treat recurrent and metastatic urachal adenocarcinoma with some success [7]. Recently, the combination of GEM/CDDP has become a new standard treatment in metastatic urothelial bladder cancer based on randomized trials showing similar survival but a more favorable toxicity profile [8]. Moreover, Bellmunt *et al.* reported a higher response rate and a better survival benefit after GEM/CDDP plus PTX chemotherapy compared to GEM/CDDP chemotherapy [9]. We have also reported a survival benefit of salvage surgery for metastatic urothelial cancer patients after GEM/CDDP or GEM/CDDP plus PTX chemotherapy [10]. That is why we introduced GCP chemotherapy for recurrence and metastasis after the CPT-11 plus CDDP chemotherapy. PET-CT showed a complete response, and a pathological examination at total

cystourethrectomy also revealed a nearly complete response. Moreover, CT showed complete deletion of the lung metastasis after a rechallenge with GCP chemotherapy. These results were much better than we expected. This is the first report of the use of GCP chemotherapy not only as a salvage chemotherapy but also as a rechallenge regimen for metastatic urachal cancer including a neuroendocrine component. In the absence of a standard chemotherapeutic regimen, GCP chemotherapy might be considered for the treatment of advanced urachal cancer including a neuroendocrine component.

## References

1. Sheldon CA, Clayman RV, Gonzalez R, Williams RD and Fraley EE: Malignant urachal lesions. *J Urol* (1984) 131: 1-8.
2. Ashley RA, Inman BA, Sebo TJ, Leibovich BC, Blute ML, Kwon ED and Zincke H: Urachal carcinoma: Clinicopathologic features and long-term outcomes of an aggressive malignancy. *Cancer* (2006) 107: 712-720.
3. Yazawa S, Kikuchi E, Takeda T, Matsumoto K, Miyajima A, Nakagawa K and Oya M: Surgical and chemotherapeutic options for urachal carcinoma: report of ten cases and literature review. *Urol Int* (2012) 88: 209-214.
4. Tran B and McKendrick J: Metastatic urachal cancer responding to FOLFOX chemotherapy. *Can J Urol* (2010) 17: 5120-5123.

5. Saijo N: Progress in treatment of small-cell lung cancer: role of CPT-11. *Br J Cancer* (2003) 89: 2178-2183.
6. Funahashi H, Miyai H, Wakasugi T, Ishiguro H, Matsuo Y, Kimura M and Takeyama H: Successful combination chemotherapy with irinotecan hydrochloride and cisplatin for primary gastric small cell carcinoma: report of a case. *World J Sur Oncol* (2013) 11: 263-268.
7. Miyata Y, Sagara Y, Matsuo T, Ohba K, Takahashi H, Sakai H and Kanetake H: Response of recurrent urachal cancer to gemcitabine and cisplatin therapy: A case report and literature review. *Anticancer Research* (2011) 31: 2335-2338.
8. Von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Sanchez Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Gruel CM and Conte PF: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* (2000) 17: 3068-3077.
9. Bellmunt J, von der Maase H, Mead GM, Skoneczna I, Santis MD, Daugaard G, Boehle A, Chevreau C, Paz-Ares L, Laufman LR, Winquist E, Raghavan D, Marreaud S, Collette S, Sylvester R and de Wit R: Randomized Phase III Study Comparing Paclitaxel/Cisplatin/Gemcitabine and Gemcitabine/Cisplatin in Patients With Locally Advanced or Metastatic Urothelial Cancer Without Prior Systemic Therapy: EORTC Intergroup Study 30987. *J Clin Oncol* (2012) 30: 1107-1113.
10. Bekku K, Saika T, Kobayashi Y, Kishimoto R, Kanbara T, Nasu Y and Kumon H: Could salvage surgery after chemotherapy have clinical impact on cancer survival of patients with metastatic urothelial carcinoma? *Int J Clin Oncol* (2013) 18: 110-115.