Response of Recurrent Urachal Cancer to Gemcitabine and Cisplatin Therapy: A Case Report and Literature Review

YASUYOSHI MIYATA, YUJI SAGARA, TOMOHIRO MATSUO, KOJIRO OHBA, HAJIME TAKAHASHI, HIDEKI SAKAI and HIROSHI KANETAKE

Department of Nephro-Urology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, Japan

Abstract. *Urachal cancer is a rare malignancy and the standard treatment is surgical resection. The prognosis of recurrent and metastatic urachal cancer is extremely poor because there is no established chemotherapy regimen. Here, the response of one patient with recurrent urachal cancer to combination chemotherapy of gemcitabine (GEM) and cisplatin (CDDP) (GC) is described. And the chemo- and radio-therapeutic regimens available for such patients are reviewed. A 67-year-old man diagnosed with stage IIIA urachal cancer underwent complete surgical resection. However, pelvic recurrence was detected on computed tomography (CT) 5 months after surgery. GC therapy was started immediately and resulted in a pronounced reduction in pelvic mass after three cycles. However, a follow-up CT scan taken 5 months later showed growth of the pelvic mass and new liver metastasis. He received GC therapy again, which resulted in reduction of the pelvic and liver metastatic masses after two cycles. However, the patient refused another course of GC therapy due to severe side-effects. Subsequent progression of the disease included spread in both regions, followed by death 16 months after recurrence. Various treatment strategies offer relatively long survival of patients with urachal cancer including those with recurrence and metastasis. Although further studies are necessary to determine its therapeutic efficacy, GC therapy may be a useful option in the treatment of urachal tumors, including recurrent tumours.*

Urachal cancer is an uncommon neoplasm reported to account for less than 1% of all bladder carcinomas and 0.01% of all neoplasms in adults (1). Although its pathogenesis is not fully understood, adenocarcinoma is common and the majority of patients are males in the fifth and sixth decades of life (2). The main form of treatment for this cancer is partial (segmental) or radical cystectomy with *en bloc* resection of the median umbilical ligament up to the umbilicus (3). On the other hand, several reports have shown that chemotherapy and/or radiation therapy can induce objective anticancer efficacy at least in some cases (4, 5); however, there is no standard chemotherapeutic regimen. The prognosis of patients with urachal cancer is generally considered to be poor due to advanced disease stage at diagnosis and high frequency of recurrence after primary treatment. In particular, the outcome of patients with recurrent urachal cancer is extremely poor (6, 7). In this report, a case of recurrent urachal cancer with pelvic, liver and lymph node metastases treated successfully with a combination of cisplatin (CDDP) and gemcitabine (GEM) is described.

Case Report

A 67-year-old man was referred to our hospital with a one-month history of asymptomatic gross hematuria. The medical history included appendectomy at the age of 19 years. Physical examination revealed a soft supra-pelvic mass. Cystoscopy detected a non-papillary mass at the bladder dome, which was later diagnosed as adenocarcinoma by biopsy. Magnetic resonance imaging (MRI) and computed tomography (CT) scan (Figure 1A) revealed a 3×4 cm mass extending from the bladder dome to the median umbilical ligament. There were no abnormal findings regarding lymph nodes, other organs and bone, as confirmed by various imaging examinations. The mass was diagnosed as adenocarcinoma of urachal origin and radical cystectomy with urachal remnant resection was performed. The tumour was confirmed to be adenocarcinoma by histo-pathological examination (Figure 2). The cancer cells extended to the bladder, but spared the abdominal wall and peritoneum (stage IIIA urachal cancer according to Sheldon *et al.'s* classification (1)). Adjuvant therapy was not applied. Five months after surgery, a solid mass was detected behind the pubis (Figure 1B) together with lymph node involvement. Accordingly, the patient received three cycles of GEM and CDDP (GC)

Correspondence to: Yasuyoshi Miyata, MD, Ph.D., Department of Nephro-Urology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Tel: +81 958197340, Fax: +81 958197343, e-mail: int.doc.miya@m3.dion.ne.jp

Key Words: Urachal cancer, recurrence, gemcitabine, cisplatin, chemotherapy.

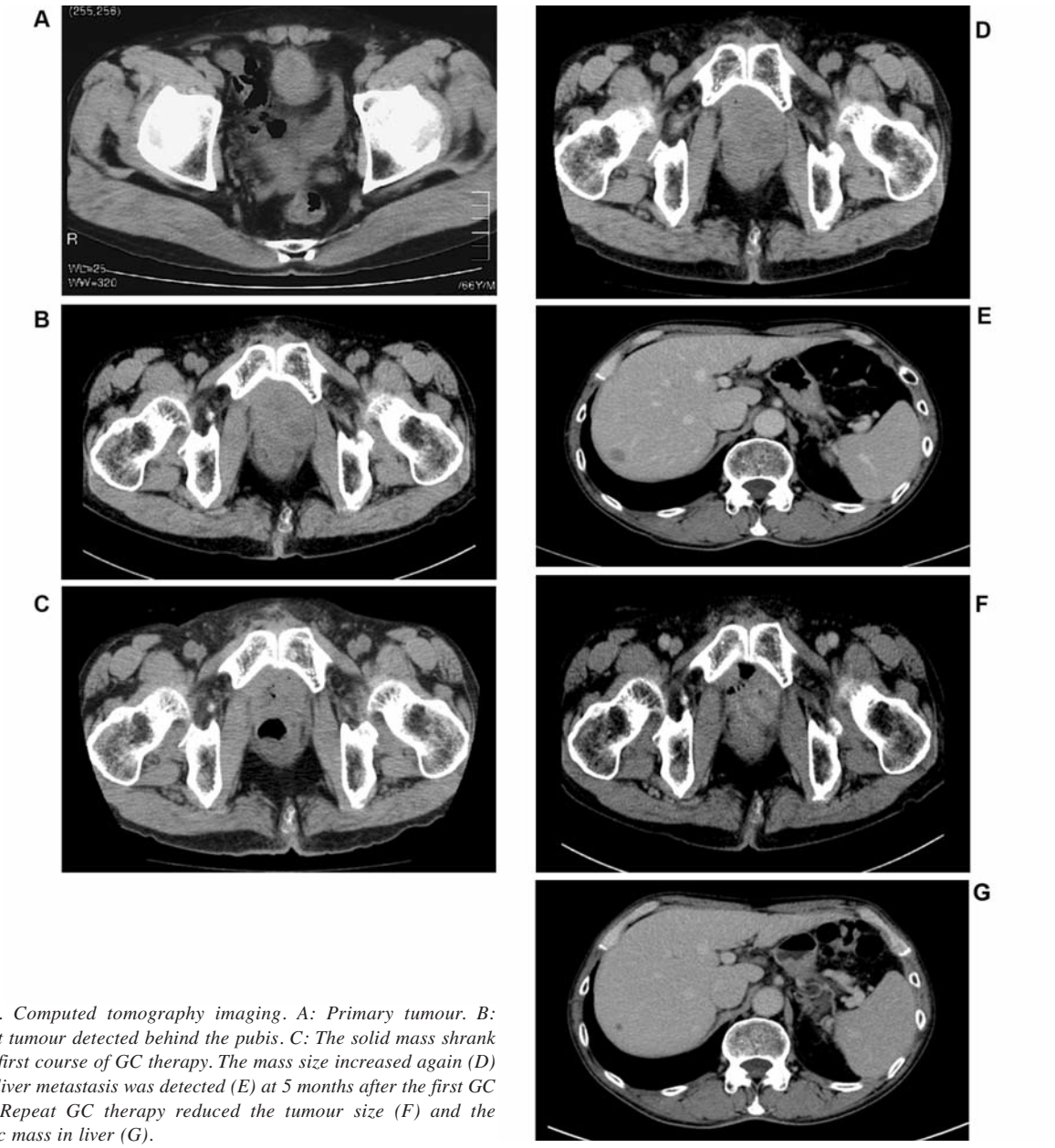

Figure 1. *Computed tomography imaging. A: Primary tumour. B: Recurrent tumour detected behind the pubis. C: The solid mass shrank after the first course of GC therapy. The mass size increased again (D) and new liver metastasis was detected (E) at 5 months after the first GC therapy. Repeat GC therapy reduced the tumour size (F) and the metastatic mass in liver (G).*

therapy with (GEM 1,700 mg on days 1, 8, and 15; CDDP 120 mg on day 2 of each 28-day cycle). Completion of this chemotherapy resulted in a pronounced reduction in pelvic mass size (Figure 1C) and resolution of lymph node swelling. However, the patient suffered from severe nausea and fatigue despite treatment with various anti-emetic agents and steroids. Accordingly, he was treated with GEM only (at 1/4w) for 5 months by ambulatory care. After the completion of therapy, the CT scan showed enlargement of the pelvic mass and new liver metastases (Figure 1D and E, respectively). At that stage, the patient requested another course of GC therapy, and two cycles of a modified GC therapy (GEM 1600 mg on days 1 and 8; CDDP 110 mg on day 2 of each 28-day cycle) were provided. This resulted in a significant resolution of the pelvic and liver metastatic tumours (Figure 1F), as well as the metastatic liver mass (Figure 1G). Another cycle of GC therapy was recommended, but the patient refused due to the appearance of severe side-effects. Two months later, there was progression of the disease in both regions. In spite of combination chemotherapy of GEM and paclitaxel (1,000 mg and 100 mg, respectively on day 1 and 8 of each 28-day 3-cycle), the patient died 16 months after recurrence.

Table I. *Treatment and prognosis of patients with recurrent urachal cancer.*

Recurrence site	Chemotherapeutic agent	Op/Rad	Outcome	Ref.
LN, Bone	5-FU+MMC+MTX	No/Yes	Survival for 19 months	17
Local*	Intra-arterial 5-FU	Yes/No	No recurrence for 23 months	18
Bone	MVAC	No/Yes	Death after 15 months	7
Urethra	None	Yes/No	No recurrence for 15 months	19
Local*	MVAC	No/No	Symptom-free for 13 months	20
LN, Bone, Ovary	None	No/Yes	Alive with tumor for 2 months	21
Bone	None	Yes/No	Disease-free for 6 months	13
Local*, LN, Lung	S-1+CDDP	Yes/Yes	Disease-free for 30 months	22
Local*, Bone, Ovary	5-FU+LV+L-OHP¶	Yes/No	Death after 37 months	12
Lung	CPT-11	No/No	Reduced by 60%	23
Local*	IFX+TXL+CDDP	Yes/No	Disease-free for 36 months	3
Lung	None	Yes/No	Disease-free for 120 months	3
Local*	5-FU+CPT-11+LV	No/No	Disease-free for 6 months	24
Lung	DXR+MMC+CDDP	No/Yes	Disease-free for >120 months	4

*Bladder, remnant, and/or pelvic tumor. ¶Followed by intraperitoneal hyperthermic chemotherapy (IPHC) with MMC. Op: operation after recurrence; Rad: radiation therapy after recurrence; MVAC: methotrexate+vinblastine+doxorubicin+CDDP; CDDP: cisplatin; LV: folinate; L-OHP: oxiliplatin; CPT-11: irinotecan; IFX: ifosfamide; TXL: paclitaxel; DXR: doxorubicin.

Discussion

Local recurrence has been reported to occur in 15-18% of urachal carcinomas within the first 2 years of follow-up (3, 8). Similar to the primary tumour, the most effective treatment for recurrent urachal cancer is considered to be surgical resection. In fact, one study reported that after surgical resection, 4 out of 6 (66.7%) patients with local recurrence and no metastasis exhibited a 15-year cure (8). Reviewing the literature of studies on the prognosis of patients with local recurrence (pelvis, bladder, remnant) six studies (Table I) showed only four patients who underwent surgical resection and three of them had relatively long disease-free survival (23, 30 and 36 months). Thus, the most important factor for prolonged survival seems to be complete surgical resection of recurrent tumours (4, 9). On the other hand, the recurrence rates of distant metastasis are high (30-40%) (3, 8). The most commonly reported sites for distant metastasis are the liver, lymph nodes, lungs, and bones (3). Actually, the current patient showed metastases in all of the aforementioned sites before death. Although prognosis is significantly affected by tumour stage, differentiation and histopathological type, advanced stage seemed to be the strongest predictor of poor prognosis (10, 11) and, patients with stage IV urachal cancer have extremely poor survival (6, 8). Thus, the management of metastatic tumours is important.

As shown in Table I, salvage surgery is often performed in patients with recurrent metastatic disease, but the role of surgery in the management of metastatic urachal cancer remains unclear. Some patients have received both surgery and another anticancer treatment modality, but a little information on the efficacy and long-term outcome was reported (8, 12). One patient with an isolated recurrent bone metastasis, treated with surgical resection only showed no metastatic disease at 6 months postoperatively, but no information on long-term outcome was presented (13). In general, data on the effect of surgical resection on prolongation of survival is limited in patients with multiple metastases. Various chemotherapeutic and radiation therapy regimens have been used in these patients (3, 6, 8). In one case (Table I), one radiomonotherapy irradiation focused on recurrent metastases in the ovaries, inguinal lymph nodes and acetabulum, and the patient remained alive with tumor at 6 months postoperatively (corresponding to 2 months after recurrence), but long-term survival and the effects of surgery were not reported. Thus, the clinical anticancer effect of radiation monotherapy for recurrent urachal tumor is speculated to be minimal. On the other hand, several reports have described the outcome of chemotherapy for metastasis and recurrent urachal cancer. The use of platinum-containing

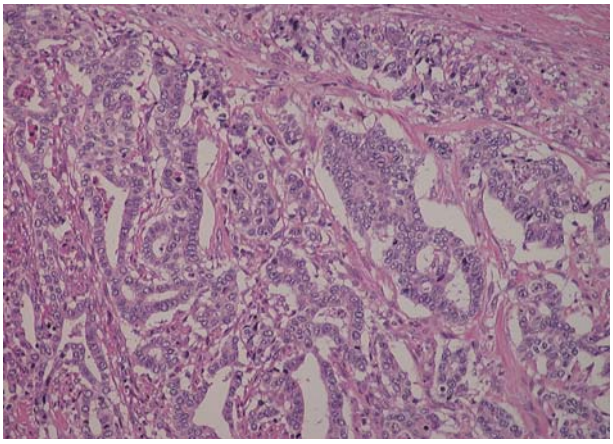

Figure 2. *Histopathological examination showing an adenocarcinoma (haematoxylin and eosin, ×200).*

regimens produced stable disease or partial response in 71% of the patients (6). After salvage therapies including CDDP-based regimens in 29 patients with metastasis two of the patients were free of disease at the time of reporting after a follow-up period of over 4 years (8). Interestingly, one of these regimens was a combination of CDDP and GEM. However, details of the chemotherapeutic regimen, patients' characteristics and course of progression were unfortunately not included. Thus, one cannot conclude that GC therapy suppresses the growth of all urachal carcinomas regardless of their malignant aggressiveness and behavior, especially since liver metastasis appeared after the first GC therapy in the present case. However, we speculate that GC-based chemotherapy has anticancer effects, at least in reducing tumour volume. Histopathologically, urachal adenocarcinoma are often described to be similar to gastric and colon adenocarcinomas. Chemotherapy regimens that include irinotecan have been reported to be efficacious for metastatic gastric and colorectal carcinoma (14, 15). In addition, colon cancer-specific FOLFOX-based chemotherapy has been used for metastatic urachal cancer with some success (12, 16). A single patient with urachal cancer who presented with multiple metastases was treated by *en bloc* resection of the urachus with partial cystectomy and lymphadenectomy, followed by adjuvant chemotherapy (CDDP, 5-FU, and DXR). DXR, and VP-16 as well as 5-FU, CDDP and interferon-α and showed no evidence of disease for more than 11 years after the initial treatment (4). Thus, the use of a combination of various treatment modalities to improve prognosis and survival of patients with recurrent urachal cancer seems warrented.

In conclusion, GC therapy seems effective in reducing the incidence of recurrence of urachal cancer. In the absence of a standardized chemotherapeutic regimen various treatment strategies show some effectiveness in urachal cancer.

Conflict of Interest

All Authors declare no conflict of interest.

References

1 Sheldon CA, Clayman RV, Gonzalez R, Williams RD and Fraley EE: Malignant urachal lesions. J Urol *131*: 1-8, 1984.

2 Grignon DJ, Ro JY, Ayala AG, Johnson DE and Ordonez NG: Primary adenocarcinoma of the bladder: a clinicopathologic analysis of 72 cases. Cancer *67*: 2165-2172, 1991.

3 Herr HW, Bochner BH, Sharp P, Dalbagni G and Reuter VE: Urachal carcinoma: contemporary surgical outcomes. J Urol *178*: 74-78, 2007.

4 Kawakami S, Kageyama Y, Yonese J, Fukui I, Kitahara S, Arai G, Hyouchi N, Suzuki M, Masuda H, Hayashi T, Okuno T and Kihara K: Successful treatment of metastatic adenocarcinoma of the urachus: report of a case with more than 10-year survival. Urology *58*: 462iv-462vi, 2001.

5 Siefker-Radtke AO, Gee J, Shen Y, Wen S, Daliani D, Millikan RE and Pisters LL: Multimodality management of urachal carcinoma: the M.D. Anderson Cancer Center experience. J Urol *169*: 1295-1298, 2003.

6 Molina JR, Quevedo JF, Furth AF, Richardson RL, Zincke H and Burch PA: Predictor of survival from urachal cancer. A Mayo Clinic study of 49 cases. J Urol *110*: 2434-2440, 2007.

7 Mohanti BK, Kumar L, Biswal BM, Lai P, Rath GK, Padhy AK, Vijayaraghavan M and Sharma MC: Aggressive bone metastases in urachal carcinoma. Urol Int *57*: 132-134, 1996.

8 Ashley RA, Inman BA, Sebo TJ, Leibovich BC, Blute ML, Kwon ED and Zincke H: Urachal carcinoma: clinicopathological features and long-term outcomes of an aggressive malignancy. Cancer *107*: 712-720, 2006.

9 Tomita K, Tobisu K, Kume H, Fujimoto H and Kakizoe T: Long survival with extended surgery for urachal carcinoma involving adjacent organs. J Urol *159*: 1298, 1998.

10 Nakanishi K, Kawai T, Suzuki M and Torikata C: Prognostic factors in urechal adenocarcinoma. A study in 41 specimens of DNA status, proliferating cell-nuclear antigen immunostatining, and argyrophilic nuclear-organizer region counts. Hum Pathol *27*: 240-247, 1996.

11 Santucci RA, True LD and Lange PH: Is partial cystectomy the treatment of choice for mucinous adenocarcinoma of the urachus? Urology *49*: 536-540, 1997.

12 Trastour C, Desprez B, Delotte J, Bongain A, Rahili A, Bernard JL and Benchimol D: Ovarian metastases from an urachal adenocarcinoma. Eur J Obstet Gynecol Reprod Biol *125*: 143-144, 2006.

13 Taylor S, Bacchini P and Bertoni F: An isolated vertebral metastasis of urachal adenocarcinoma. Arch Pathol Lab Med *128*: 1043-1045, 2004.

14 Bouche O, Raoul JL, Bonnetain F, Giovannini M, Etienne PL, Lledo G, Arsène D, Paitel JF, Guérin-Meyer V, Mitry E, Buecher B, Kaminsky MC, Seitz JF, Rougier P, Bedenne L and Milan C; Fédération Francophone de Cancérologie Digestive Group: Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancérologie Digestive Group Study –FFCD9803. J Clin Oncol *22*: 4319-4328, 2004.

15 Hurwitz HI, Fehrenbacher L, Hainsworth JD, Heim W, Berlin J, Holmgren E, Hambleton J, Novotny WF and Kabbinavar F: Bvacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. J Clin Oncol *23*: 3502-3508, 2005.

16 Tran B and McKendrick J: Metastatic urachal cancer responding to FOLFOX chemotherapy. Can J Urol *17*: 5120-5123, 2011.

17 Quilty PM: Urachal carcinoma: a response to chemotherapy. Br J Urol *60*: 372, 1987.

18 Hatch TR and Fuchs EF: Intra-arterial infusion of 5-fluorouracil for recurrent adenocarcinoma of bladder. Urology *33*: 311-312, 1989.

19 Yasui T, Okamura T, Akita H, Kojima M and Kohri K: Urethral recurrence of an urachal carcinoma: a case report. Int J Urol *4*: 106-108, 1997.

20 Ichiyanagi O, Sasagawa I, Suzuki Y, Iijima Y, Kubota Y, Nakada T and Arai S: Successful chemotherapy in a patient with recurrent carcinoma of the urachus. Int Urol Nephrol *30*: 569-573, 1998.

21 Ohira S, Shiohara S, Itoh K, Ashida T, Fukushima M and Konishi I: Urachal adenocarcinoma metastatic to the ovaries: case report and literature review. Int J Gynecol Pathol *22*: 189-193, 2003.

22 Kojima Y, Yamada Y, Kamisawa H, Sasaki S, Hayashi Y and Hohri K: Complete response of a recurrent advanced urachal carcinoma treated by S-a/cisplatin combination chemotherapy. Int J Urol *13*: 1123-1125, 2006.

23 Kume H, Tomita K, Takahashi S and Fukutani K: Irinotecan as a new agent for urethral cancer. Urol Int *76*: 281-282, 2006.

24 Mohile SG, Schleicher L and Petrylak DP: Treatment of metastatic urachal carcinoma in an elderly woman. Nat Clin Pract *5*: 55-58, 2008.

Received March 19, 2011
Revised May 23, 2011
Accepted May 24, 2011