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# Female urethral diverticular carcinoma treated by multimodality therapies: A case report

Koichi Uemura [a, *], Kenta Yoshida [a], Masahiro Inoue [a], Nobuhiko Mizuno [a], Takayuki Murakami [a], Takashi Kawahara [c], Hiroji Uemura [c], Jiro Kumagai [b], Futoshi Tsuchiya [a]

[a] Department of Urology, Yokohama Red Cross Hospital, Yokohama, 231-8682, Japan
[b] Department of Pathology, Yokohama Red Cross Hospital, Yokohama, 231-8682, Japan
[c] Departments of Urology and Renal Transplantation, Yokohama City University Medical Center, Yokohama, 232-0024, Japan

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## 1. Introduction

Primary urethral diverticular carcinoma is uncommon in women, accounting for less than 1% of genitourinary malignancies. Patients present with non-specific and overlapping clinical symptoms such as difficulty urinating, pain on urination, incontinence and hematuria. No standard treatment is available at present due to the rarity of this disease. We herein report a rare case of urethral diverticular carcinoma in a woman that was treated with surgery, radiotherapy and chemotherapy.

## 2. Case presentation

A 58-year-old woman presented with complaints of difficulty urinating and pain on urination. She had a few years' history of episodes of pollakiuria and dysuria. A physical examination revealed a movable, soft, nontender mass 3 cm in size protruding from the anterior vagina wall. Magnetic resonance imaging (MRI) revealed a cystic formation around the urethra (Fig. 1a), and urethrography showed a diverticulum surrounded the urethra on all sides (Fig. 1b).

Under the diagnosis of urethral diverticulum, we performed transvaginal diverticulum excision as completely as possible. Aspiration cytology of the diverticulum was negative, and the histopathological diagnosis of the diverticular wall was no malignancy. However, her symptoms worsened postoperatively. MRI was performed again, revealing a residual diverticulum with internal heterogeneity (Fig. 1c). We suspected a urethral diverticular abscess and performed abdominal residual diverticulum excision. Contrary to our expectations, an intraoperative frozen section analysis of the specimen revealed high grade urothelial carcinoma predominated by adenocarcinoma component (Fig. 1d).

We decided to perform radical cystectomy later because the lesion was unresectable by diverticulum excision alone. Positron emission tomography-computed tomography revealed bilateral pelvic lymph node metastases (Fig. 2a). The levels of the tumor markers (CA19-9, CEA) decreased to within the normal range. Under the diagnosis of primary urethral diverticular adenocarcinoma, we eventually conducted radical cystectomy and urethrectomy with combined partial resection of the vagina and pelvic lymph node excision four months after the first visit to our department. The range of lymph node excision was closure, external and internal iliac lymph nodes. The patient's urinary tract was reconstructed using an ileal conduit. She was discharged from our hospital after 4 weeks without any complications. A pathological analysis of the resected specimen revealed 55% well-differentiated adenocarcinoma, 40% squamous cell carcinoma, and 5% urothelial carcinoma of urethral diverticulum without invasion to the bladder neck or

* Corresponding author.
*E-mail addresses:* megumayaneyan@yahoo.co.jp (K. Uemura), 12wayne06@gmail.com (K. Yoshida), soulmasa521@yahoo.co.jp (M. Inoue), mizuno.nobuhiko@gmail.com (N. Mizuno), t-murazo@wb3.so-net.ne.jp (T. Murakami), takashi_tk2001@yahoo.co.jp (T. Kawahara), hu0428@yokohama-cu.ac.jp (H. Uemura), kumagai.path@yokohama.jrc.or.jp (J. Kumagai), tsuchiya.uro@yokohama.jrc.or.jp (F. Tsuchiya).

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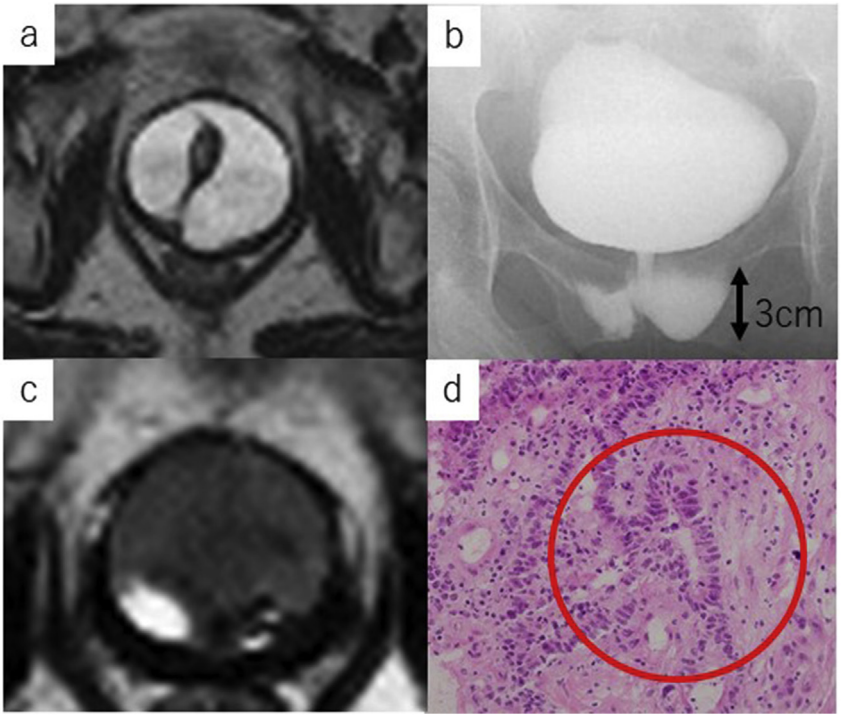


**Fig. 1.** (a):Axial view of cystic formation around the urethra on T2-weighted magnetic resonance imaging of the pelvis. (b): Urethrography showed a urethra diverticulum which size was 3cm. (c).Axial view of the residual diverticulum with internal heterogeneity on T2-weighted magnetic resonance imaging of the pelvis. (d): An intraoperative frozen section analysis of the specimen revealed adenocarcinoma.

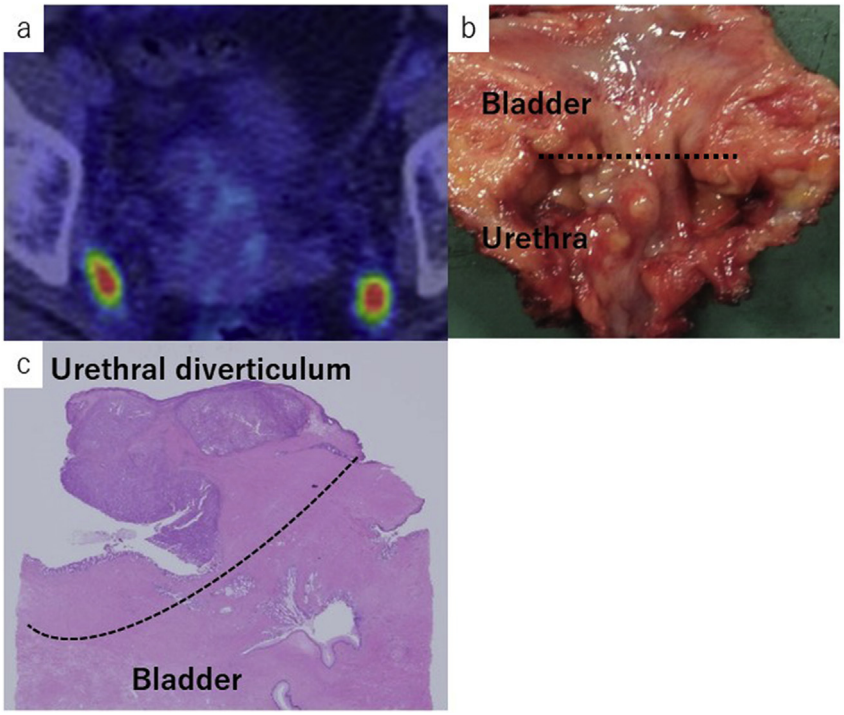


**Fig. 2.** (a)Positron emission tomography-computed tomography revealed bilateral pelvic lymph node metastases.(b)(c)A surgical specimen showed the tumor in the urethral diverticulum area and no bladder neck invasion. The microscopic findings of the resected specimen were mixed types of tumor consisting of adenocarcinoma, squamous cell carcinoma and urothelial carcinoma.

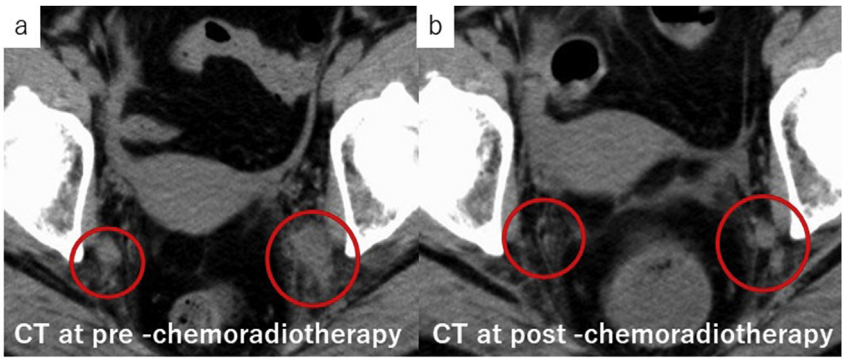


**Fig. 3.** (a)(b) After radiotherapy and two courses of chemotherapy, computed tomography showed a partial response of the enlarged lymph nodes in the pelvis under the RECIST guidelines.

vaginal muscle layer (pT2N1, Grade 3, INFb, ly1, v1; Fig. 2b and c).

Computed tomography at one month after the operation showed bilateral enlargement of the internal iliac lymph nodes. We performed postoperative adjuvant external beam radiotherapy (EBRT) with adjuvant chemotherapy (gemcitabine 1000 mg/m$^2$ on days 1 and 8 and nedaplatin 70 mg/m$^2$ on day 1). After radiotherapy and 2 courses of chemotherapy, the enlarged lymph nodes had shrunk by 50% (partial response [PR] under the RECIST guidelines) (Fig. 3a and b). No evidence of residual tumor progression has been found in the eight months since radical cystectomy.

## 3. Discussion

Some cases have been reported carcinoma of the female urethral diverticulum until now. The most common histological type in female urethral diverticular tumor is reported by some to be adenocarcinoma, accounting for about 60% of cases, while others describe squamous cell carcinoma to be the most common, accounting for about 70% of cases.[1] Grigsby et al. found that the tumor size and histology of female urethral diverticular carcinoma were independent prognostic factors for the survival or local control and reported that adenocarcinoma had a relatively poor prognosis.[2]

Regarding the treatment, local excision, such as diverticulectomy or urethrectomy, followed by more aggressive surgery, such as radical cystectomy or anterior pelvic exenteration, has frequently resulted in local recurrence and the appearance of distant metastases. Rajan et al.[3] suggested that anterior pelvic exenteration is generally recommended for local excision. In advanced cases, combined modality therapy with chemoradiotherapy and salvage surgery is recommended for improving the local control rate and the overall survival.

In the present case, a preoperative diagnosis of urethral diverticular cancer was difficult because of her nonspecific presentation and the imaging findings. We have no chemotherapy regimens for bladder adenocarcinoma, and no reports have described effective regimens for bladder adenocarcinoma. We therefore performed surgery without any neoadjuvant chemotherapy in advance despite the pelvic lymph node swelling and lack of distant metastases. The pathological findings of the resected specimen were 55% well-differentiated adenocarcinoma, 40% squamous cell carcinoma and 5% urothelial carcinoma of urethral diverticulum. She had a low kidney function (serum creatinine: 1.78 mg/dl), so we selected gemcitabine and nedaplatin (GN therapy) instead of gemcitabine and cisplatin (GC therapy) as a salvage therapy.

Von der Maase et al. suggested strengthening the role of gemcitabine and cisplatin as a standard of care for patients with locally advanced or metastatic urothelial carcinoma.[4] Nedaplatin is associated with less renal toxicity and a lower incidence of gastrointestinal complications than cisplatin. Nedaplatin is a second-generation platinum complex developed in Japan that exerts its anti-tumor effect by inhibiting DNA duplication. Some reported that GN therapy improved the survival of patients with advanced urothelial carcinoma. Furthermore, Ota et al. reported that GN therapy was more effective than GC therapy against squamous cell carcinomas, such as esophageal cancer, lung cancer and cervical cancer.[5] At our institute, because of the low renal toxicity of nedaplatin, for patients with a low renal function, gemcitabine and nedaplatin are used instead of gemcitabine and cisplatin. In the present case, the postoperative pathological diagnosis showed a specimen that was 40% squamous cell carcinoma and 5% urothelial carcinoma, so we chose GN therapy as the adjuvant chemotherapy. After radiotherapy and two courses of GN therapy, the enlarged lymph nodes had reached PR. We intend to administer two more courses of GN therapy following computed tomography from now on.

Female urethral diverticular carcinoma is a rare disease and is difficult to diagnose in patients with a non-specific presentation. We recommend imaging analyses such as MRI, CT or UG for women whose urinary symptoms persist or worsen despite medication.

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