Resection of a retroperitoneal cancer of unknown primary site after chemoradiation therapy: a case report

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Case report

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Abstract

Background: Complete recovery from retroperitoneal squamous cell carcinoma of unknown primary site treated by multidisciplinary therapy is extremely rare. Case presentation: A 78-year-old man was referred to our hospital due to a mass measuring 8 cm in size in the left pelvic retroperitoneal area, which was diagnosed as a cancer of unknown primary site. The pathological type was squamous cell carcinoma. The left iliac artery/vein and ureter were involved in the tumor, and the tumor caused severe left leg pain. Although inflammation and symptoms were severe, palliative radiotherapy was considered. After that, biweekly combined therapy with docetaxel, cisplatin, and fluorouracil was planned. After 5 courses of chemotherapy, the tumor diameter reduced from 11.6 cm to 4 cm in size. In addition, the border between the iliac vessels, urinary tract and tumor became apparent. The patient underwent radical resection of the tumor 8 months after the treatment started. The left ureter and the external/internal iliac artery were preserved, but the external iliac vein was sacrificed because of the possibility of tumor invasion. The postoperative course was free of complications, and the patient was discharged 10 days after the operation. The histopathological findings showed no residual viable tumor cells or foreign body-type giant cells with necrosis. The pathological effect of chemotherapy was defined as Grade 3 (pathological complete response). The patient has experienced no recurrence or distant metastasis for 4 years. Conclusions: Multidisciplinary therapy succeeded in treating a retroperitoneal squamous cell carcinoma of unknown primary site with preservation of organ function.

Background

Cancer of unknown primary site (CUP) is defined as a histologically proven metastatic malignant tumor whose primary site cannot be identified during pretreatment evaluation [1]. These tumors are not rare; they represent 3–5% of all malignancies diagnosed in oncology practice. However, squamous cell carcinoma of unknown primary site (SCCUP) is a relatively rare malignant tumor [2]. Moreover, although these patients are usually treated with aggressive multidisciplinary therapy similar to patients with locally advanced head and neck cancer, the expected median survival time in previous reports is only 6–9 months [1, 2]. We report a case of SCCUP located in the retroperitoneum that was treated with multidisciplinary therapy and in which long survival was obtained without recurrence.

Case Presentation

A 78-year-old man was referred to the Department of Surgical Oncology, Gifu University Hospital due to a mass measuring 8 cm in size in the left pelvic retroperitoneal area that was causing left leg pain. Computed tomography (CT) showed that the left iliac artery/vein and ureter seemed to be involved in the mass. Ureteral dilatation due to obstruction of the ureter by the mass was also observed (Fig. 1). Fluorine-18 fluorodeoxyglucose positron emission tomography showed no other focus with increased glucose metabolism, which excluded other origins of carcinoma or any metastatic location except the left pelvic mass (Fig. 2). Even after further studies such as esophagogastroduodenoscopy, colonoscopy, and cystoscopy, we could find no other primary lesion. Endoscopic ultrasound-guided fine needle aspiration

was performed during colonoscopy. Immunohistochemical studies (Fig. 3) showed positive epithelial markers in pan-cytokeratin AE1/AE3 with differential expression of cytokeratin 7 rather than cytokeratin 20. However, leukocyte common antigen and S100 were negative. The origin of the tumor could not be detected. Laboratory data revealed a high level of C-reactive protein at 8.99 mg/dL, white blood cell count of 30,450/μL, squamous cell carcinoma antigen (SCC Ag) of 11.1 ng/mL and prostate-specific antigen of 9.629 ng/mL. Based on these results, he was diagnosed as having SCCUP. Because the mass aggravated his symptoms, he was started on palliative radiotherapy before inducing chemotherapy. After he started radiation therapy, the pain in his left leg improved. Although he needed to start chemotherapy immediately, we were concerned about renal dysfunction due to the left ureteral stenosis and performed a left nephrostomy before chemotherapy. Combined chemotherapy with paclitaxel and carboplatin was chosen as the first-line treatment according to the National Comprehensive Cancer Network (NCCN) clinical guideline, but infusion reaction occurred after injection of the paclitaxel. Therefore, he needed to be changed to a regimen without paclitaxel, and we chose combined chemotherapy of biweekly docetaxel, cisplatin and 5-fluorouracil (5FU) (Bi-DCF). After five courses of Bi-DCF, the tumor diameter had decreased from 11.6 cm to 4 cm in size. In addition, the border between the iliac vessels, ureter and tumor became apparent (Fig. 4). Tumor marker SCC Ag had decreased to within normal range. So, radical resection was performed 8 months after starting treatment. The left urinary tract and the external/internal iliac artery were preserved, but the external iliac vein was sacrificed at the time of surgery because of the possibility of tumor invasion (Fig. 5). His postoperative course was without complications, and he was discharge from hospital 10 days after surgery. One month after surgery, the left nephrostomy was closed because his ureter function was maintained. The histopathological findings showed only necrotic tissue or fibrotic changes, and there were no residual viable tumor cells. The pathological effect of chemotherapy was defined as complete response (Fig. 6). The patient has experienced no recurrence or distant metastasis for 4 years.

Discussion

CUP is a histologically proven metastatic malignant tumor with a primary site that cannot be identified during pretreatment evaluation [1]. CUP, with its variety of biological characteristics, accounts for 3–5% of all malignancies, approximately 50% of which are diagnosed as well- to moderately differentiated metastatic adenocarcinoma, 30% as undifferentiated or poorly differentiated carcinoma, 15% as SCC and the remaining 5% as undifferentiated neoplasms [2].

A detailed medical history and physical findings are important for diagnosis, followed by various examinations such as blood biochemical tests including tumor markers, chest X-ray and whole-body CT [2, 3]. Furthermore, if tumor tissue can be collected, immunohistochemical staining is necessary for exclusion of occult primaries and for suggesting tissues of origin [4].

CUP remains an extremely aggressive disease with a poor prognosis. The median survival time is between 4 and 12 months [2, 5], and select patients with favorable subsets of CUP have median overall survival times ranging from 12 to 36 months [6]. It is thought that more than half of patients with CUP

have multiple lesions [7], and chemotherapy has a main role in the treatment of CUP. Although no regimen has been established as a standard first-line therapy [8, 9], a combination of platinum plus taxane-based chemotherapy obtained a superior response rate and survival in the reported phase II trials [8, 10–12]. However, multiple phase II studies have found no superior combination of cytotoxics, and there remains no standard second-line therapy [9].

Radiation therapy is also an option for localized tumors. In some cases, radical irradiation may be considered, and in others, palliative treatment. In the present case, although it was necessary to begin chemotherapy immediately, there was concern about renal dysfunction due to the left ureteral stenosis. Therefore, a left nephrostomy was performed before chemotherapy to preserve his renal function. Besides, left leg pain due to the tumor was severe, and palliative radiation therapy was started for a total of 10 Gy before the induction of chemotherapy. Furthermore, because radiation monotherapy could also cause metastasis, it was essential that the patient begin early systemic chemotherapy, and he initially underwent combination therapy of weekly paclitaxel plus carboplatin. However, because of the infusion reaction caused by the paclitaxel at the first injection, a different combination regimen of taxane plus platinum was needed. Thus, the patient was administered Bi-DCF chemotherapy [13],, which is used for advanced esophageal squamous cell carcinoma in our institution, after ethics committee approval was received.

A regimen combining docetaxel, cisplatin and 5FU is also used for esophageal cancer, gastric cancer and head and neck cancers, and is also described in the NCCN guidelines. It offers a prolonged prognosis compared to conventional cisplatin plus 5FU combination therapy although there is concern about renal dysfunction [14–17]. Hara et al. also reported that the same regimen was used as preoperative chemotherapy for esophageal cancer, with a response rate of 64%, Grade 3/4 leukopenia of 45% and neutropenia of 83% [18]. In our institution, we performed Bi-DCF therapy as neoadjuvant chemotherapy for esophageal cancer and reported Grade3/4 leukopenia of 12.5%, neutropenia of 31.4%, and no instances of renal dysfunction while maintaining a high response rate of 90.3% compared with previous reports [19]. Bi-DCF therapy can be safely performed even in patients with potential high risk of renal dysfunction such as in this case, and it is thought that high effects can be expected.

Although there is no unified opinion regarding surgical treatment for CUP, it is often considered when a single, resectable tumor is present. If the tumor can be resected without tumor remnants, a favorable prognosis can be expected.

In the present case, tumor shrinkage due to chemotherapy following palliative radiotherapy was obtained and clarified the margin between the tumor and iliac artery, vein and ureter. Therefore, surgical treatment could be performed without tumor remnants although the left external iliac vein was sacrificed because of suspected tumor invasion. Moreover, the resected tissue was fibrous tissue with extensive necrosis without viable cells, and granulation formation and the accumulation of foamy histiocytes were observed. All of these were changes that occurred due to the therapeutic effect after the tumor was reduced in size. The patient has experienced no recurrence or distant metastasis for 4 years.

Conclusions

We report a rare case of SCCUP in which an outstanding outcome was achieved. CUP remains an extremely aggressive disease, so early diagnosis and multidisciplinary therapy including radiation therapy, chemotherapy and radical surgery should be considered while maintaining organ function and the general condition of the patient.

Abbreviations

5FU: 5-fluorouracil, Bi-DCF: biweekly docetaxel, cisplatin and 5-fluorouracil combined chemotherapy, CT: computed tomography, CUP: cancer of unknown primary site, NCCN: National Comprehensive Cancer Network, SCC Ag: squamous cell carcinoma antigen, SCCUP: squamous cell carcinoma of unknown primary site

Declarations

Ethical declarations

Ethical approval

The authors comply with the ethical standards of WJSO and obtained informed consent from the patient included in this study.

Consent for publication

Consent for publication was obtained from the patient included in this study.

Availability of data and materials

All data generated or analyzed are included in this published article

Competing interests

K. Yoshida has received grants, personal fees and nonfinancial support from Chugai Pharmaceutical Co., Ltd. during the conduction of the study; grants and personal fees from Taiho Pharmaceutical Co., Ltd., Pfizer Inc., and Yakult Honsha Co., Ltd.; grants from Bristol-Myers Squibb; grants from Kyowa Hakko Kirin Co., Ltd. outside the submitted work; honoraria from Taiho Pharmaceutical Co., Ltd., Pfizer Inc., Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Yakult Honsha Co., Ltd.; and had a consultant or advisory relationship with Taiho Pharmaceutical Co., Ltd. and La Roche, Ltd. T. Takahashi has received honoraria for lectures from Takeda Pharmaceutical Co., Ltd. All remaining authors declare that they have no conflict of interest.

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None

Authors' contributions

Study conception and design: TS and NM. Acquisition of data: TS, NM, TT, MF, YI, IY, TI, HI, YT, NO, KYa, and KYo. Analysis and interpretation of data: TS and NM. Drafting of manuscript: TS and NM. Critical revision: TS, NM, and KYo. Supervision: KYo.

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Figures

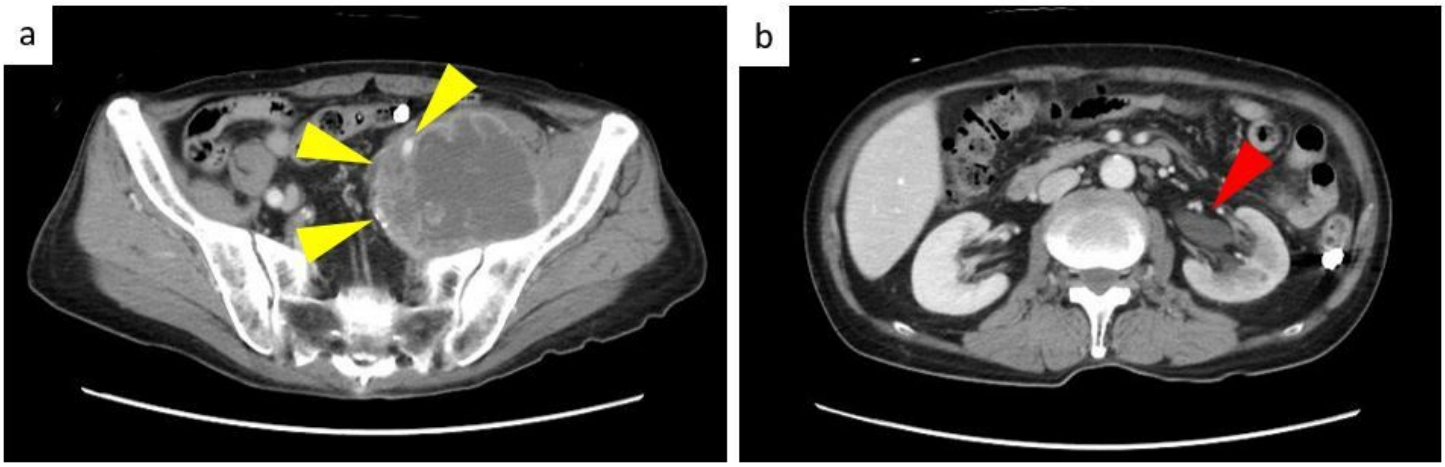

Figure 1

Computed tomography images of the tumor. (a) The left iliac artery/vein and ureter were involved in the tumor (yellow arrowheads). (b) Left ureteral dilatation due to obstruction of the ureter by the mass was observed (red arrowhead)

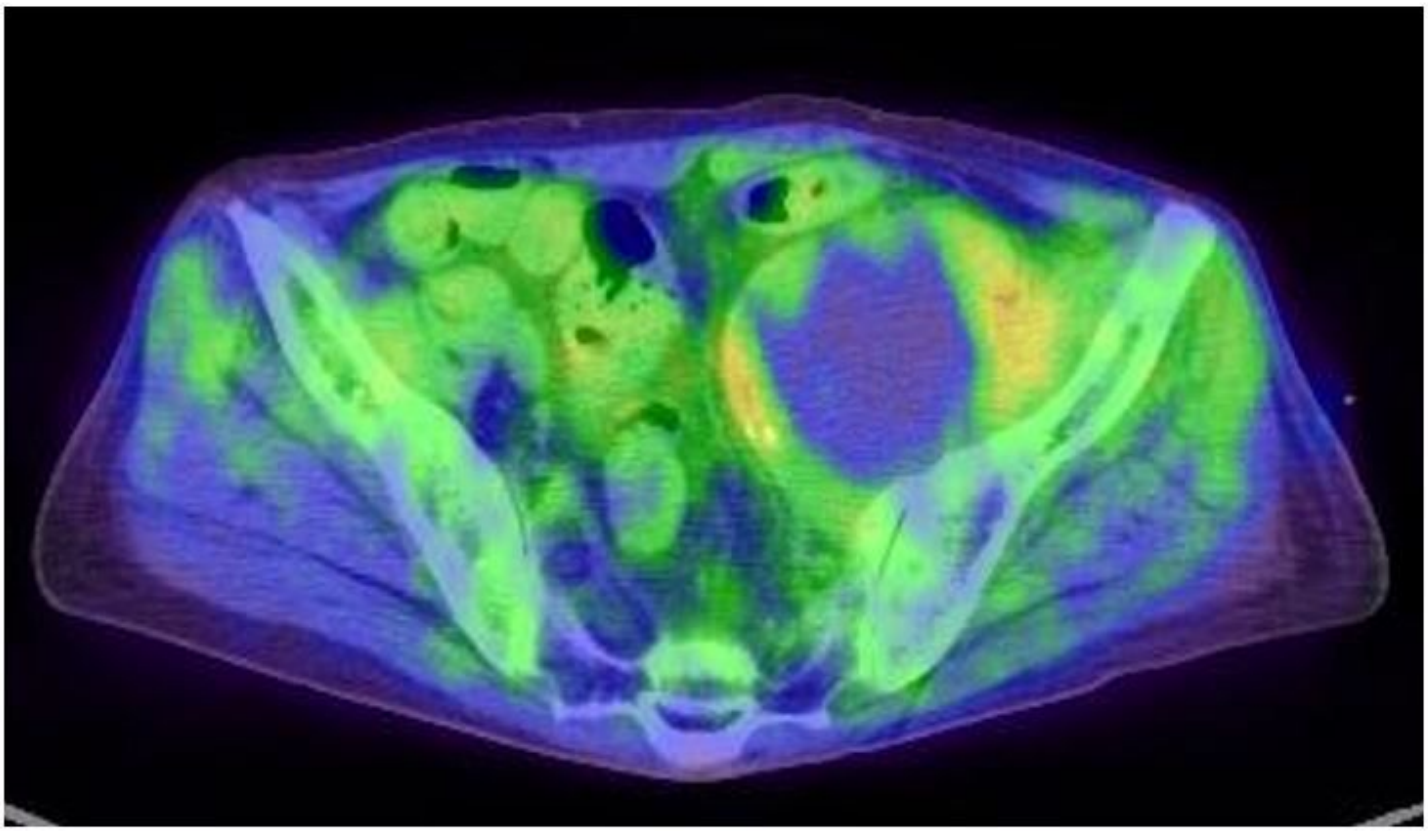

Figure 2

FDG concentration was observed in the tumor (standard uptake value max: 2.86)

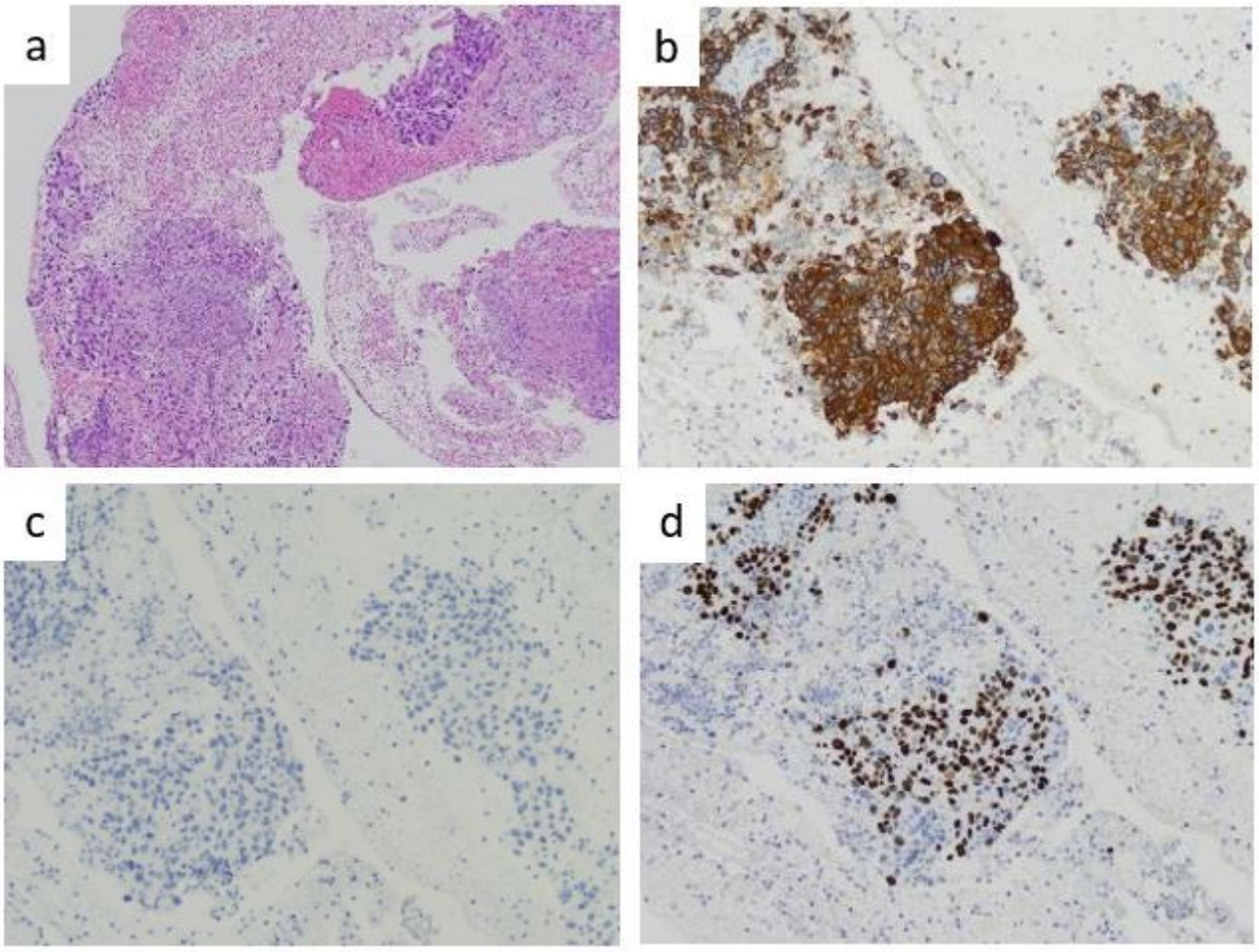

Figure 3

(a) Photomicrograph showing the tissue of the left pelvic mass with large and hyperchromatic nuclei (hematoxylin-eosin stain; ×40). (b) The tissue as immune-stained with Cytokeratin 7. The lesions containing malignant cells were well stained (×100). (c) The tissue immune-stained with Cytokeratin 20. The lesions containing malignant cells were not stained (×100). (d) Tissue immune-stained with p63. The lesions containing malignant cells were not stained (×100). These findings indicated poorly differentiated squamous cell or urothelial carcinoma, but it was difficult to infer the primary lesion

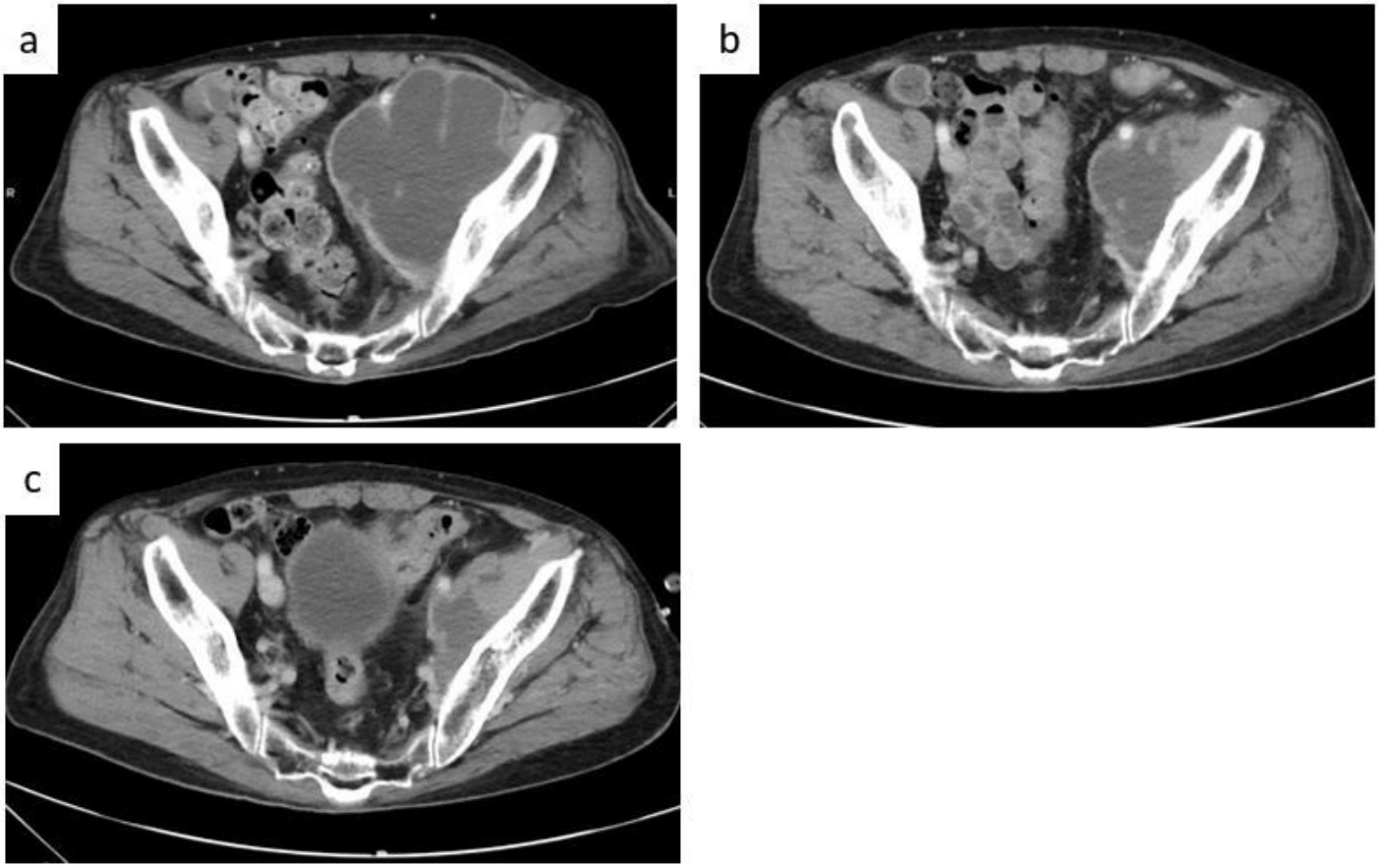

Figure 4

(a) Computed tomography (CT) findings 1 month after the start of treatment. The CT value inside the tumor had decreased. (b) CT findings 3 months after the start of treatment. The tumor had gradually shrunk in size. (c) CT findings 7 months after the start of treatment. The tumor had continued to shrink, and boundaries between the tumor and iliac vessels and the ureter became apparent

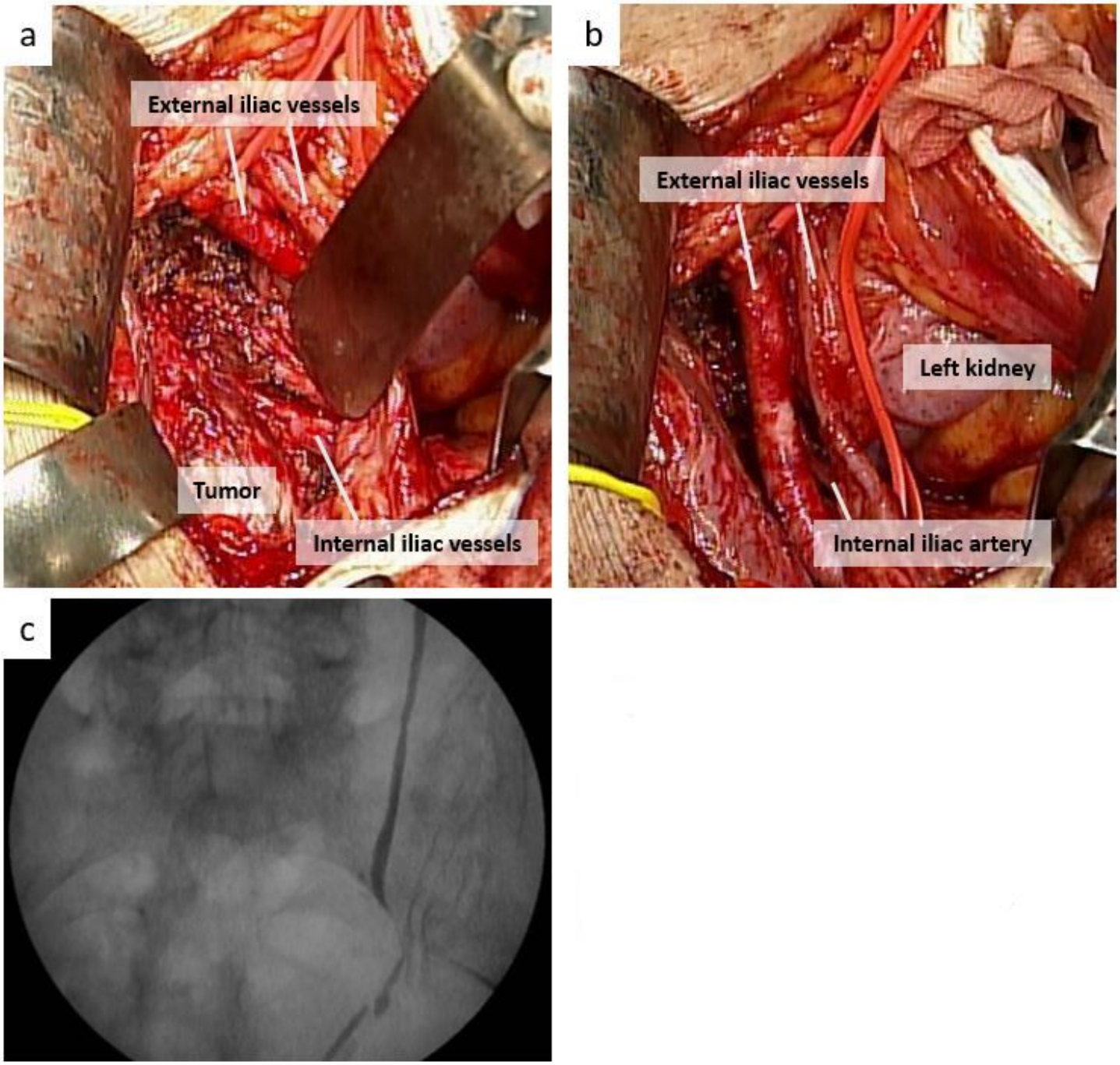

Figure 5

Surgical findings. (a) The tumor identified via extraperitoneal approach from the left pelvic wall. The tumor was dorsal to the external iliac vessels and clearly demarcated from the external iliac vessels. (b) After tumor resection, the external iliac vessels and internal iliac artery were preserved, but the iliac vein was sacrificed because of the possibility of tumor invasion. The ureter was preserved (yellow vessel tape) (c) Intraoperative urography. The left ureter was displaced by the tumor, but the tumor had not directly invaded the ureter, and the ureter was preserved without injury

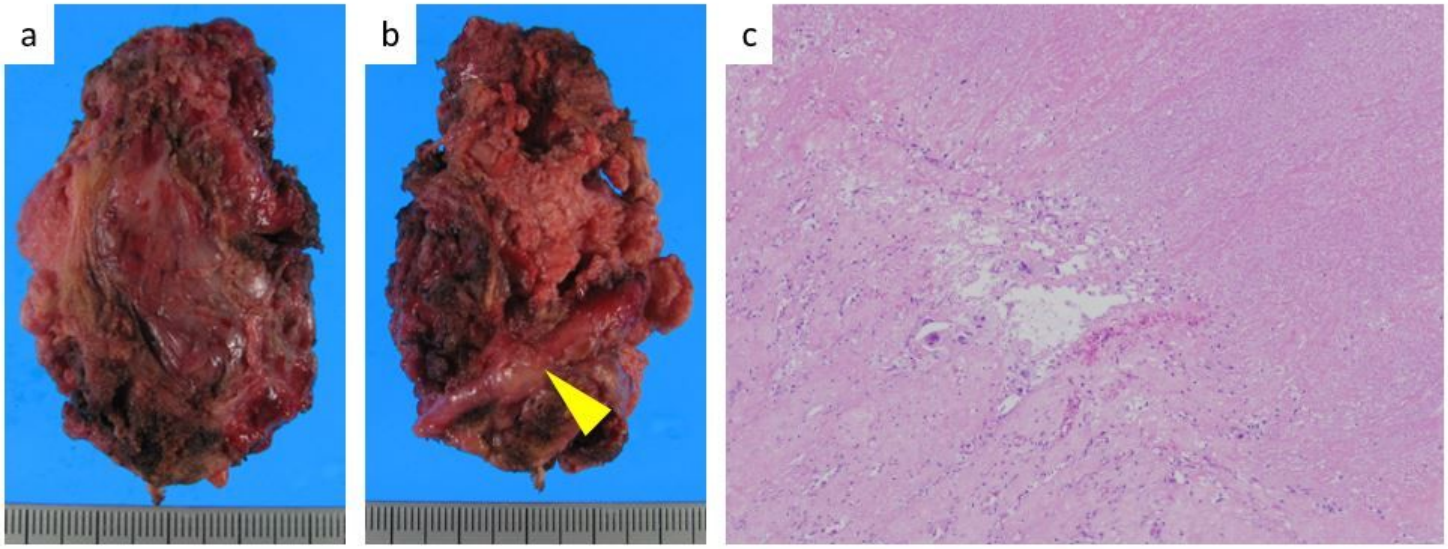

Figure 6

(a) Resected specimen of the tumor (abdominal side). (b) Resected specimen of the tumor (dorsal side). The sacrificed internal iliac vein is observed (yellow arrowhead) (c) Hematoxylin-eosin staining of the resected specimen (×40). Pathological findings showed extensive necrosis and fibrotic changes with granulation and histiocytes; there were no residual viable tumor cells