



# Primary signet ring cell carcinoma of uterine cervix and related disease: two case reports and a review

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## Abstract

Primary signet ring cell carcinoma of uterine cervix (SRCCC) is extremely rare. We present two cases of primary SRCCC that were treated with robot-assisted laparoscopic radical hysterectomy (RALRH). Case 1 had stage IB2 cervical adenocarcinoma, in which signet ring cell (SRC) was predominant. As adjuvant chemotherapy was not successful, she twice underwent surgical excision of recurrent tumors in pararectal lymph node and periureteral space 11 months and 27 months after RALRH, respectively. There were only SRCs observed in recurrent tumors. Case 2 had stage IB1 cervical adenocarcinoma, in which SRCs were detected only in the biopsy specimen, and no relapse occurred at 15 months after RALRH. PET/CT was useful for tumor detection in both cases, and the amount of SRC components was associated with the prognostic outcome. Considering the high recurrence rate and few complications at secondary surgery, minimally invasive surgery would be preferred as the primary surgery for SRCCC.

**Keywords** Cervical cancer · Signet ring cell carcinoma · Robot-assisted laparoscopic radical hysterectomy

## Introduction

Primary signet ring cell carcinoma of uterine cervix (SRCCC) is very rare, and most SRCCCs are metastatic; the stomach, colon, breast, appendix, lung, ovary, gallbladder, and bladder are possible primary sites. In particular, an extremely rare entity is primary cervical adenocarcinoma comprising pure or predominant signet ring cells (SRCs). To date, there have been only a few cases of primary SRCCC reported in the literature. Since most of these reports lack long-term follow-up, the clinical significance of SRCCC remains unclear, and its diagnosis is challenging as the proportions of the SRC component are various. Thus, to clarify the clinical features of this disease, we report two cases of

primary SRCCC treated with robot-assisted laparoscopic radical hysterectomy (RALRH) together with a literature review.

## Case 1

A 40-year-old multiparous woman presented to our hospital with abnormal vaginal bleeding. Pelvic examination revealed a 6-cm mass in the cervix without parametrial involvement. Histopathological examination revealed adenocarcinoma, though the tumor subtype was undetermined. Magnetic resonance imaging (MRI) exhibited the 58-mm mass in the cervix, and increased fluorodeoxyglucose (FDG) uptake on positron-emission tomography (PET)/computed tomography (CT) was observed (Fig. 1a). Among the serum tumor markers, CA125, CEA, and SCC were elevated (122.6 U/mL, 92.9 ng/mL and 3.6 ng/mL, respectively). The diagnosis of cervical adenocarcinoma, stage IB2, was made.

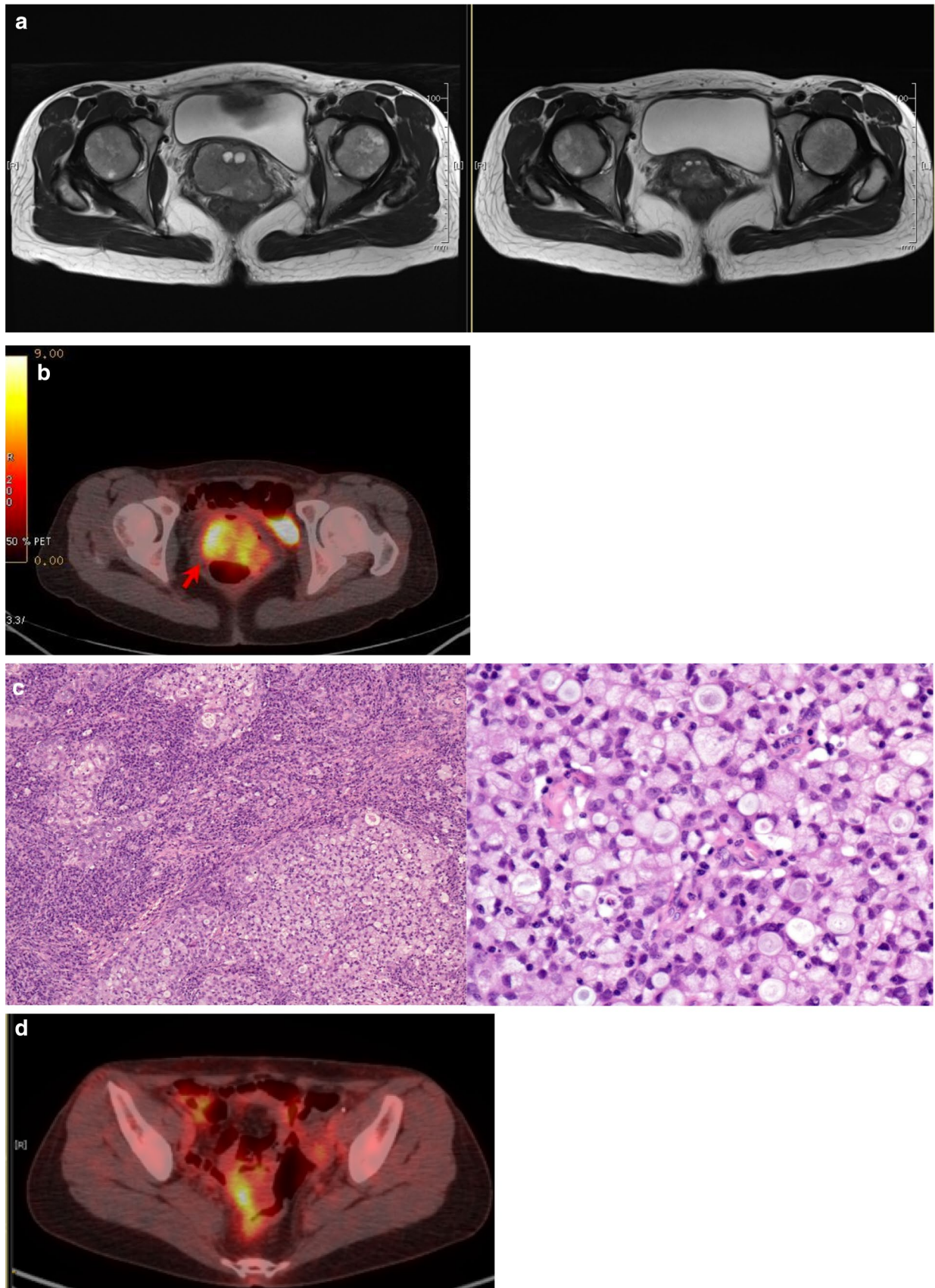
As the tumor shrunk from 58 to 38 mm in diameter after two cycles of chemotherapy with cisplatin and paclitaxel (Fig. 1b), RALRH was performed. Microscopically, the cervical tumor predominantly contained SRCs, and 3 out

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◀ **Fig. 1** Images of SRCCC in case 1 and case 2. **a** Increased uptake of FDG was observed on PET/CT imaging of case 1 (SUVmax: 12.8). **b** A 58-mm cervical mass on T2-weighted imaging decreased in volume to 38 mm after two cycles of chemotherapy in case 1. **c** The primarily resected tumor comprised predominant signet ring cells in case 1. **d** PET/CT imaging shows increased uptake of FDG in the pararectal lymph node at the time of recurrence in case 1 (SUVmax: 4.9). **e** The secondary resected tumor consisted of signet ring cells, which was identical to the primary tumor in case 1. **f** CT could not detect definite tumor, but increased FDG uptake was observed in right periureteral region. **g** Signet ring cells of the same features involved ureteral wall in case 1. **h** The biopsy specimen revealed adenocarcinoma with signet ring cell components in case 2. **i** Increased uptake of FDG was observed on PET/CT imaging of case 2 (SUVmax; 8.9). **j** The surgical specimen revealed the usual type of adenocarcinoma without evidence of SRCC in case 2

of 20 pelvic lymph nodes and parametrial tissues had SRC involvement (ypT2bN1, Fig. 1c). She received four additional cycles of chemotherapy. At 10 months after surgery, relapse occurred in a pararectal lymph node, with increased FDG uptake on PET/CT (Fig. 1d) and serum CEA elevation (6.7 ng/mL). Surgical excision was performed to confirm the recurrence of SRCCC (Fig. 1e). Because of the positive surgical margin, the patient underwent post-operative chemotherapy with cisplatin, paclitaxel, and bevacizumab. At 15 months after the secondary surgery, CT revealed no definite tumor, but increased FDG uptake was observed in right periureteral region (SUVmax: 4.4, Fig. 1f) with serum CEA elevation (63.5 ng/mL). Third tumor excision was performed, and SRC involvement into the ureteral wall was microscopically observed (Fig. 1g).

## Case 2

A 44-year-old multiparous woman was referred to our hospital for cervical adenocarcinoma with SRC components (Fig. 1h). The 20-mm tumor in the cervix was detected on MRI, showing increased uptake of FDG on PET/CT (Fig. 1i). RALRH was performed under the diagnosis of cervical cancer stage Ib1. Microscopically, the tumor consisted of endocervical adenocarcinoma, but the SRC component was not observed in the surgical specimen (Fig. 1j). The diagnosis of cervical adenocarcinoma, usual type (pT1bN0), was confirmed. She did not receive any adjuvant therapy, and there was no relapse at 15 months after surgery.

## Discussion

SRCCC is defined in the current histopathological classification of World Health Organization (WHO 2014) as mucinous carcinoma, signet ring cell type, which shows SRC differentiation focally to diffusely. There have been only 22 cases of primary SRCCC reported in the literature to date, not including present cases (Table 1). Carcinoma with signet ring cell morphology arises more commonly in the gastrointestinal tract or breast. Therefore, metastasis from these organs should be carefully ruled out. In our cases, both PET/CT and MRI showed no evidence of possible primary sites other than the cervix. As most SRCCCs are HPV related [1, 2], our two cases were block-positive for p16 immunostaining.

The rarity of this disease makes its diagnosis difficult. SRCCC in a pure or predominant form is extremely rare, and SRCCC usually coexists with the usual endocervical type or intestinal type [1]. In case 1, as SRCs were predominant in recurrent tumors as well as the primary surgical specimen, recurrence was confirmed. In case 2, on the other hand, the SRC components were present only in the biopsy specimen. The WHO definition suggests a diagnosis of SRCCC can be made with the presence of SRC components. Among previous reports, six cases were diagnosed as SRCCC with the biopsy specimen alone (Table 1). Therefore, although case 2 should be diagnosed as the usual type of adenocarcinoma in the surgical specimen, this case might be regarded as SRCCC-related disease.

The clinical significance of the SRC components in case 2 is unclear. In SRC carcinomas in other sites, SRC histology has been designated as a poor prognostic factor. However, recent studies have shown that SRC histology in gastric cancer is not necessarily associated with a poor prognostic outcome, especially at early stage [3, 4]. This is also true in primary SRCCC. Patients with stage I disease showed relatively long disease-free survival times (Table 1) and were more likely without recurrence ( $p < 0.05$ , Table 2a), and those treated with surgery showed significantly better survival ( $p < 0.001$ , Table 2b). In contrast, those at advanced stage showed poor prognoses because complete excision was difficult and most SRCCCs were resistant to chemotherapy or radiotherapy. Therefore, surgical excision should be considered as the first choice not only in primary treatment but also at the time of recurrence. In case 1, solitary recurrence occurred twice in a pararectal lymph node and periureteral

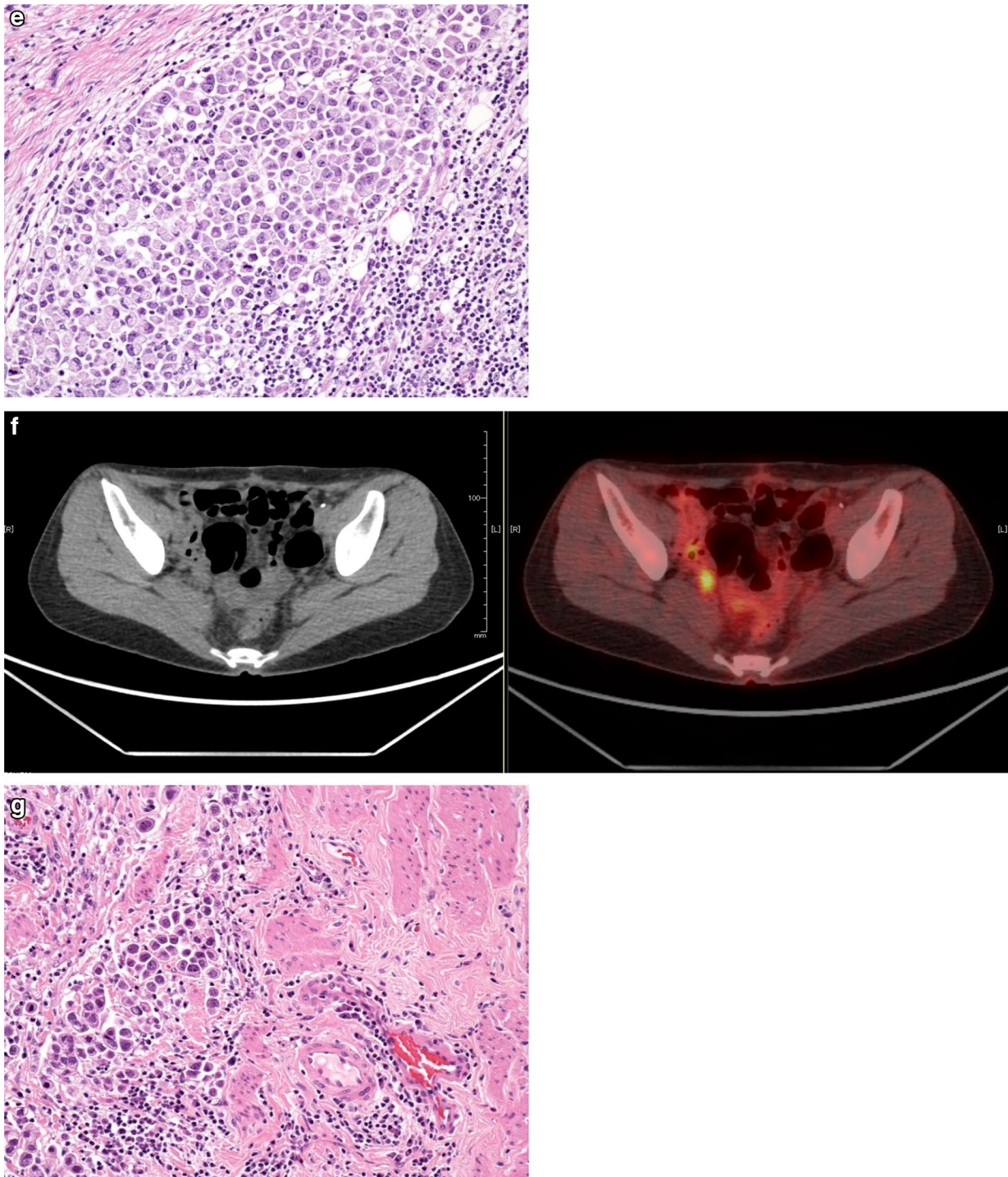


Fig. 1 (continued)

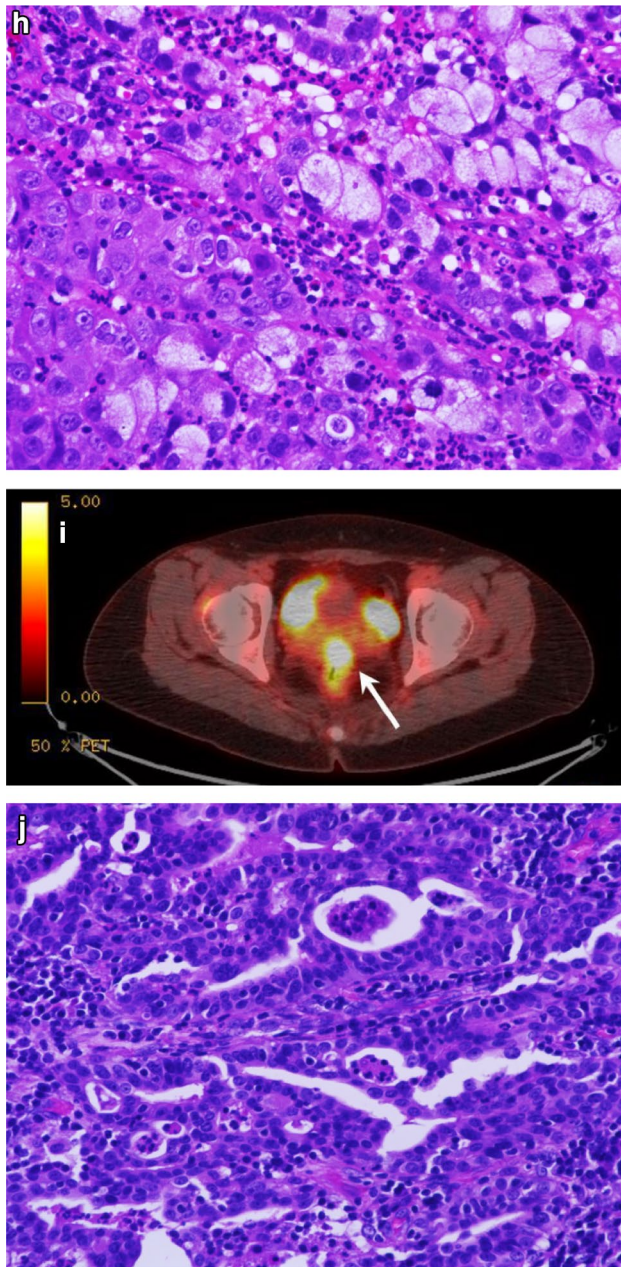


Fig. 1 (continued)

fossa even with chemotherapy, but successful excision was achieved at both times.

Increased uptake of FDG was observed on PET/CT not only in the present two cases but also in all six previously reported SRCCC cases who had undergone PET/CT (Table 1). PET/CT exhibits lower sensitivity in gastric SRC carcinoma (poorly cohesive adenocarcinoma) possibly due to low cellularity, intracellular mucin, and scarce expression of glucose transporter 1 (GLUT-1) [5]. In case 1, SRCs exhibited cohesive solid growth pattern, which might be one reason why FDG uptake was relatively high since GLUT-1 overexpression is accompanied with cohesive type of gastric carcinoma [6]. These findings imply that SRCCC might harbor different metabolic characteristics including GLUT-1 expression, resulting in the usefulness of PET/CT for detecting ambiguous recurrence in case 1. Nevertheless, further investigation is necessary to designate the usefulness of PET/CT for detecting SRCCC as the SRC component was scarce in case 2 and the number of SRCCC cases to undergo PET/CT is still small.

RALRH is reported superior to abdominal radical hysterectomy in terms of lower blood loss, a shorter hospital stay, and less frequent wound-related and febrile morbidities in early-stage cervical cancer [7], and this superiority of RALRH is kept after neoadjuvant chemotherapy for stages IB2 to IIB [8]. In both of our cases, the excisional margin was free, the numbers of harvested nodes exceeded 20, and blood loss was 350 mL and 92 mL, which are comparable to previous reports [7, 8]. Unexpected recurrence after RALRH occurred in case 1, but there were only mild peritoneal adhesions confined to the vaginal stump at the secondary surgery. Although therapeutic intensity of RALRH is unsure as spilled tumor implants during RALRH might be the source of relapse, RALRH is still considered feasible to reduce the extent and severity of adhesions since the efficacy of chemotherapy or radiation for SRCCC is limited and surgical excision of recurrent tumor would be inevitable.

As previous reports are limited, it is hard to clarify the tumor biology of SRCCC and determine the appropriate therapeutic strategy. Nevertheless, PET/CT can be designated as useful for detection, and surgical excision would contribute to better outcomes. RALRH should be considered at primary surgery for reducing peri-operative complications and difficulties in recurrent tumor excision.

**Table 1** Reported cases of SRCC of the cervix in the literature

| Author                 | Age | Stage | Tumor size                 | MR   | PET/CT         | Treatment           | Outcome        | SRC components     |
|------------------------|-----|-------|----------------------------|------|----------------|---------------------|----------------|--------------------|
| Moll                   | 50  | III   | NA                         | NA   | NA             | Sx, RT              | DOD 10 months  | Predominant        |
| Mayorga                | 68  | IB2   | 8 cm (Ins)<br>3 cm (SS)    | NA   | NA             | NACT, Sx            | NED 35 months  | Predominant        |
| Haswani                | 74  | IB1   | 4 cm (SS)                  | NA   | NA             | Sx                  | NED 25 months  | Predominant        |
|                        | 33  | IIIB  | 5.5 cm (Ins)               | NA   | NA             | Palliative<br>RT/CT | DOD 18 months  | Predominant        |
| Cardosi                | 38  | IB1   | 3.5 cm (SS)                | NA   | NA             | Sx, RT              | NED 9 months   | Predominant        |
|                        | 53  | IB1   | NA                         | NA   | NA             | Sx, RT, CT          | NED 6 months   | Predominant        |
| Moritani               | 29  | III   | 85 mm (SS)                 | NA   | NA             | Sx, CT              | NED 6 months   | 40%                |
| Suarez                 | 80  | IIIB  | 20 mm (Ins)                | NA   | Cervix(+)      | CT + CCRT           | DOD 19 months  | NA                 |
| Insabato               | 46  | IB1   | 18 mm (SS)                 | NA   | NA             | Sx, RT, CT          | NED 8 years    | Pure               |
| McCluggage             | NA  | NA    | NA                         | NA   | NA             | NA                  | NA             | Focal              |
|                        | NA  | NA    | NA                         | NA   | NA             | NA                  | NA             | Focal              |
| Versas                 | 36  | IV    | 2 cm (Ins)                 | NA   | NA             | CT                  | DOD 7 weeks    | Focal              |
|                        | 43  | IV    | NA                         | NA   | NA             | CT                  | DOD 2 months   | Focal              |
| Lowery                 | 60  | IB1   | NA                         | NA   | NA             | RT, Sx              | NED > 10 years | NA                 |
| Balci                  | 53  | IIB   | 5 cm (Ins)                 | NA   | NA             | Sx                  | NA             | 80%                |
| Yoon                   | 47  | IB1   | 1 cm (MRI)<br>15 mm (SS)   | Done | Cervix(+)      | Sx                  | DOD 6 months   | 70%                |
| Giordano               | 45  | IIB   | NA                         | Done | NA             | Sx                  | NA             | 30%                |
| Kaidar-person          | 37  | IIB   | > 4 cm (Ins)               | NA   | Cervix, PeN(+) | CCRT, Sx            | NED 4 months   | NA                 |
| Washimi                | 31  | IIA   | 15 mm (MRI)<br>60 mm (SS)  | Done | Cervix(+)      | Sx, CT              | NED 41 months  | Pure               |
| Cracchiolo             | 64  | IVB   | 2 cm (Ins)                 | NA   | Cervix(+)      | Palliative<br>RT    | DOD 3 months   | NA                 |
| Sal [2]                | 48  | IB1   | 1.7 cm (MRI)<br>25 mm (SS) | Done | Cervix(+)      | Sx                  | NED 18 months  | 70%                |
| Doghri [1]             | 48  | IVB   | 53 mm (MRI)                | Done | NA             | none                | DOD 3 months   | NA                 |
| Hamada (present cases) | 40  | IB2   | 58 mm (MRI)<br>21 mm (SS)  | Done | Cervix(+)      | Sx, CT              | AWD 29 months  | Predominant        |
|                        | 44  | IB1   | 20 mm (MRI)<br>17 mm (SS)  | Done | Cervix(+)      | Sx                  | NED 15 months  | Focal/no SRC in SS |

SS surgical specimen, *Ins* inspection, *SRC* signet ring cell, *PeN* pelvic nodes, *Sx* surgery, *CT* chemotherapy, *NACT* neoadjuvant chemotherapy, *RT* radiotherapy, *CCRT* concurrent chemoradiotherapy, *DOD* died of disease, *NED* no evidence of disease. *NA* not available

**Table 2** The clinical impact of tumor stage and surgery: (a) the patients with stage I disease are significantly less likely to die of the disease, (b) the patients treated with surgery are significantly less likely to die of the disease

|               |              |                 |              |
|---------------|--------------|-----------------|--------------|
| (a) Stage     | I            | II >            | $p = 0.0198$ |
| DOD           | 1            | 7               |              |
| NED           | 9            | 3               |              |
| (b) Treatment | With surgery | Without surgery | $p = 0.0007$ |
| DOD           | 2            | 6               |              |
| NED           | 12           | 0               |              |

Fisher's exact test

## Compliance with ethical standards

**Conflict of interest** The authors declare no conflicts of interest.

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