

# The first case of recurrent small cell neuroendocrine carcinoma of the uterine cervix successfully treated with robotic-assisted super radical hysterectomy

Seiji Mabuchi<sup>a,\*</sup>, Keita Waki<sup>b</sup>

<sup>a</sup> Department of Gynecology, Osaka International Cancer Institute, 3-1-69, Otemae, Chuo-ku, Osaka-shi, Osaka 541-8567, Japan

<sup>b</sup> Department of Obstetrics and Gynecology, Nara Medical University, Kashihara, Nara, Japan

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## ABSTRACT

Recurrent cervical cancer occurring in a previously irradiated field is one of the most complicated challenges for gynecological oncologists. Super-radical hysterectomy is a standard procedure for laterally extended cervical tumors, particularly recurrent cervical cancer in a previously irradiated field. This potentially curative procedure is challenging to perform due to the technical complexities and lack of reproducibility. Thus, it is performed only by skilled surgeons, either via open or laparoscopic approaches wherein the entire paracervix at the pelvic wall and the hypogastric vessels are transected.

In this report, we described the first case of recurrent small cell neuroendocrine carcinoma of the uterine cervix that was successfully treated with robot-assisted super-radical hysterectomy.

## 1. Introduction

Recurrent cervical cancer occurring in a previously irradiated field is one of the most complicated challenges for gynecological oncologists. Previous investigations have suggested that recurrence is localized to the pelvis in approximately 40% of patients who have undergone prior definitive radiotherapy (Hong et al., 2004). Another report suggested that up to 17% of these patients develop central pelvic recurrence (Michael et al., 2005).

Patients with recurrent cervical cancer have a dismal prognosis if surgery or radiotherapy cannot be applied, with a reported two-year overall survival rate of approximately 20%, even with chemotherapy (Klaiber-Hakimi, 2015). In such cases with unfavorable histology, as in small cell neuroendocrine carcinoma (SCNEC), the prognosis is usually worse, and long-term survival after salvage treatment is rarely reported (Frumovitz et al., 2017).

Despite its potential as a curative treatment, re-irradiation has been employed sparingly owing to concerns of severe late toxicity (Mabuchi et al., 2014). Surgical salvage could be another curative treatment option for this patient population. Pelvic exenteration (PE) or radical

hysterectomy (RH) has been recommended to select groups of centrally recurrent or persistent cervical cancer patients, and long-term survival rates of 30–60% have been achieved (Chiva et al., 2008; Mabuchi et al., 2017). However, these usually pose surgical difficulties associated with operating on previously irradiated, hard, fibrotic tissue, even in patients with seemingly resectable lesions. Mortality rates of 0–17% after PE and severe complication rates of 30–60% after PE or RH were documented in previous studies (Chiva et al., 2008; Mabuchi et al., 2017). Moreover, these procedures cannot be applied to laterally extended cervical tumors.

For laterally extended diseases, laterally extended endopelvic resection (LEER) or super-radical hysterectomy (SRH) are curative options (Höckel et al., 2012; Kim et al., 2017). However, these procedures are associated with significant mortality, morbidity, and recovery time (Höckel et al., 2012; Kim et al., 2017) and require high competency. A laparoscopic approach has been demonstrated in an attempt to minimize invasiveness and surgery-related complications (Kanao et al., 2021), although the feasibility, safety, and efficacy of the robot-assisted approach have not been evaluated for these procedures.

This report documents the first case of successful robot-assisted SRH

**Abbreviations:** CCRT, concurrent chemoradiotherapy; CT, computed tomography; FDG, fluorodeoxyglucose; H&E, hematoxylin and eosin; LACC, laparoscopic approach to cervical cancer; LEER, laterally extended endopelvic resection; MIS, minimally invasive surgery; MRI, magnetic resonance imaging; PE, pelvic exenteration; RH, radical hysterectomy; SCNEC, small cell neuroendocrine carcinoma; SRH, super-radical hysterectomy.

\* Corresponding author.

E-mail address: [seiji.mabuchi@oici.jp](mailto:seiji.mabuchi@oici.jp) (S. Mabuchi).

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in a previously irradiated recurrent cervical SCNEC.

## 2. Materials and methods

### 2.1. Surgical procedures

A zero-degree endoscope was used for the entire procedure. Robotic surgery was performed using the da Vinci Xi Surgical System (Intuitive Surgical Inc., Sunnydale, CA, USA). To prevent the spillage of tumor cells into the peritoneal cavity, the vaginal wall was circumferentially incised 2 cm distal to the tumor, and a vaginal cuff was created by suturing the vagina over the cervix with a running suture. After this transvaginal procedure, robot-assisted SRH was initiated. The bilateral fallopian tubes were ligated using surgical clips. The round ligaments were cut, and the anterior broad ligament was opened. After the development of paravesical and pararectal spaces using gentle blunt dissection, the bilateral uterine arteries and ureters were identified. The uterine arteries were cut at their origins; subsequently, the ureters were unroofed from the retroperitoneum and uterine vessels. After identifying the cardinal ligaments, the deep uterine veins, obturator vessels, internal pudendal vessels, inferior gluteal vessels, and internal iliac vessels were identified and transected at least 1 cm away from the tumor (Fig. 2). The ureters were retracted using silicone slings as previously described (Mabuchi et al., 2020) and gently dissociated from the surrounding connective tissue. The anterior and posterior vesicouterine ligaments were then transected.

In cases requiring bilateral salpingo-oophorectomy, the infundibulopelvic ligaments were isolated, coagulated, and transected. After the uterosacral ligaments are transected, the rectum was carefully separated from the vagina. The remaining connective tissues surrounding the vagina were excised, and the uterus was disconnected. All surgical specimens were removed through the vagina.

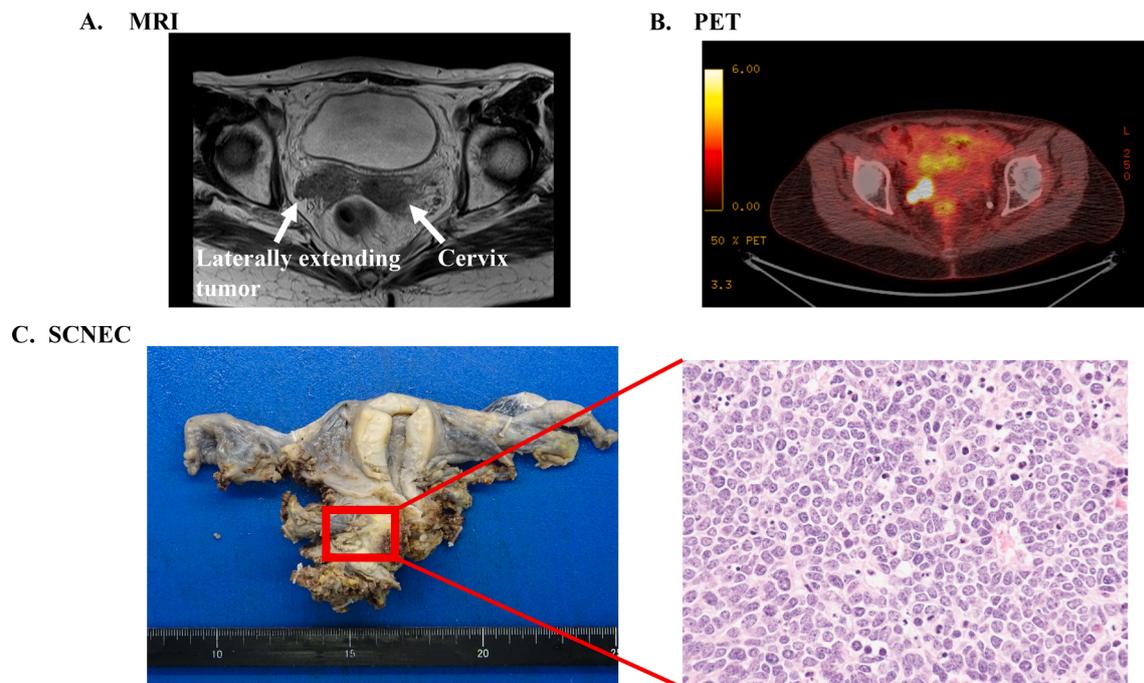
### 2.2. Informed consent statement

A written informed consent was obtained from the patient for publication of this case report and accompanying images.

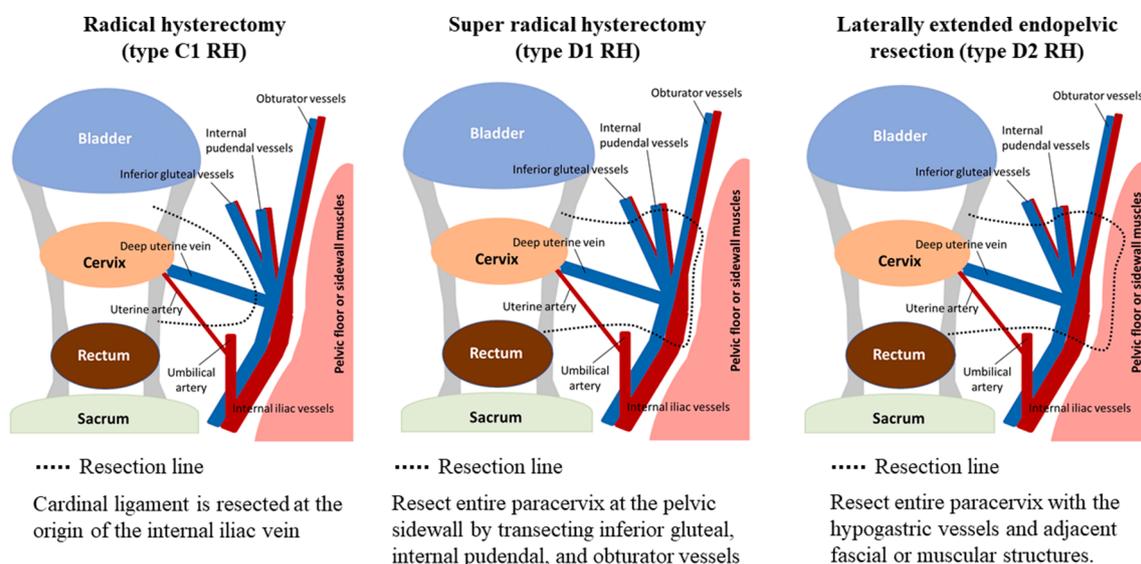
### 2.3. Case presentation

A 69-year-old Japanese woman, gravida 4 and para 2, was referred to our hospital due to abnormal vaginal bleeding. Her past medical history was remarkable for a subarachnoid hemorrhage one year ago. She underwent no previous surgical procedures. On evaluation, she was found to have a bulky cervical tumor that extended to the lower third of the vagina. Biopsies of the cervical and vaginal lesions demonstrated SCNEC. Pelvic magnetic resonance imaging (MRI) and computed tomography (CT) of the abdomen and pelvis revealed a 65 mm cervical mass with proximal parametrial extension as well as swelling of the right obturator node. The diagnosis of International Federation of Gynecology and Obstetrics stage III cervical cancer was confirmed and treated with concurrent chemoradiotherapy (CCRT) consisting of external beam radiotherapy (50 Gy in 25 fractions), high-dose rate brachytherapy (6 Gy in 3 fractions), and weekly cisplatin (40 mg/m<sup>2</sup>), which achieved a complete response.

Twelve months after CCRT, pelvic examination revealed a cervical mass with parametrial invasion. Pelvic MRI demonstrated a 35 mm pelvic tumor extending from the uterine cervix to the right inferior iliac vessels (Fig. 1A). On the left side, parametrial invasion was not evident. Fluorine-18-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) demonstrated significant FDG uptake in the laterally extended mass in the patient, but no other FDG uptake was noted (Fig. 1B). The diagnosis of locally recurrent cervical cancer was confirmed, and a super-radical hysterectomy was planned as a salvage treatment. A robot-assisted super-radical hysterectomy plus bilateral salpingo-oophorectomy was performed as the patient desired a minimally invasive approach. Although performing SRH on previously irradiated, hard, fibrotic tissue was technically challenging, the recurrent cervical tumor was completely removed using SRH on the right side and type C1 RH on the left side, without any intraoperative complications (Fig. 2 and Supplemental Video). The surgery duration was 405 min and blood loss was 130 mL; blood transfusion was not needed. Due to the postoperative peritonitis requiring antibiotic treatment, her hospitalization was prolonged, and the patient was discharged after 20 days. The resected tumor specimen showed a recurrent tumor located at the



**Fig. 1.** A. T2-weighted MRI image showing a cervical tumor that extended to the inferior iliac vessels, B. FDG-PET/CT image showing a significant FDG-uptake was observed in a laterally extended cervical tumor, C. Hematoxylin and eosin (H&E) stained sections of the tumor indicating recurrent SCNEC [x20].



**Fig. 2.** Illustrations showing the differences between a radical hysterectomy (type C1 RH), super-radical hysterectomy (type D1 RH) and laterally extended endopelvic resection (LEER; type D2 RH). Type C1-D2 RH was based on Querleu and Morrow classification (12).

parametrium extending to the inferior iliac vessels (measured  $45 \times 41 \times 30$  cm), and recurrent SCNEC was observed (Fig. 1C). The surgical margin was disease-free. The patient was alive and free of disease 8 months after surgery.

### 3. Discussion

In this report, we presented a case of recurrent cervical small cell carcinoma successfully treated with robot-assisted SRH. To our knowledge, this is the first report of robotic SRH.

Both SRH and LEER are Type D hysterectomies in the Querleu Morrow classification (Querleu et al., 2017). SRH is classified as Type D1 hysterectomy or the resection of the entire paracervix at the pelvic side wall together with the hypogastric vessels, exposing the roots of the sciatic nerve. Meanwhile, Type D2 (LEER) is the resection of the entire paracervix with the hypogastric vessels and adjacent fascial or muscular structures (Fig. 2).

Although SRH was introduced by Ryukichi Mibayashi in 1941 (Kim et al., 2017), due to technical complexities, lack of reproducibility, and concern for procedural safety, this procedure has been performed only by skilled surgical oncologists (Kim et al., 2017; Kanao et al., 2021). In our review of literature, this procedure was described only in two studies on cervical cancer patients: one was performed using the open approach (Kim et al., 2017); and the remaining two were performed via the laparoscopic approach (Kanao et al., 2021).

The advantage of robot-assisted surgery is that it offers three-dimensional vision, a human arm simulation system, and a tremor filtration system, which allow safe, stable operations and may reduce the incidence of postoperative complications. The learning curve was also reduced using robotically assisted surgery. In addition to shorter hospital stay, less postoperative pain, and less intraoperative blood loss in patients, robot-assisted laparoscopic surgery offers increased ergonomic and technical comfort to the surgeon during difficult, complicated, and prolonged operations.

In our case, the robotic system provided good visualization of the deep pelvis and allowed accurate manipulation of radiated fibrotic tissue, leading to a safe SRH procedure. The surgical time and estimated blood loss were 405 min and 130 mL, respectively. The patient required no blood transfusion during hospitalization; this result was significantly better than that of previous studies on RH, PE, or LEER performed for recurrent cervical cancer via an open approach (Chiva et al., 2008; Mabuchi et al., 2017; Höckel et al., 2012; Kim et al., 2017). In our

experience with RH via open approach in recurrent cervical cancer cases, the median surgical time, estimated blood loss, and rate of blood transfusion were 474 min, 1500 mL, and 47.0%, respectively (Mabuchi et al., 2017). As the patient suffered from postoperative peritonitis requiring antibiotic treatment, she stayed in the hospital for 20 days, which was similar to 19 days observed in our previous studies on RH, PE, or LEER performed for recurrent cervical cancer via an open approach (Mabuchi et al., 2017).

Type C1 RH, which preserved autonomic nerves including pelvic splanchnic nerve and hypogastric nerves, was performed on the left side; thus, the patient did not experience serious urinary dysfunction after SRH and could void herself without requiring self-catheterization, even after complete transection of the right hypogastric plexus during the Type D hysterectomy. Moreover, even though the patient had unfavorable histology (i.e. SCNEC) usually associated with an extremely poor prognosis, the patient was free of disease 8 months after SRH. Although the post-surgical follow up is short, based on these findings, we believe that SRH via the robotic approach is an ideal treatment option for select patients with recurrent cervical cancer with significant parametrial invasion.

Although our case suggests the safety and utility of robot-assisted SRH, we do not recommend the use of a robotic approach for recurrent cervical cancer patients without reflecting on the results of the laparoscopic approach to cervical cancer trial (LACC trial) (Ramirez et al., 2018). As the LACC trial included only newly diagnosed early-stage cervical cancers, the role of minimally invasive surgery (MIS) in all patients with recurrent cervical cancer remains undetermined. However, we believe that all cervical cancer patients scheduled to undergo MIS should be informed about the outcome of this LACC trial. Moreover, to ensure the oncologic safety of robot-assisted SRH, efforts should be taken to avoid the use of a vaginal uterine manipulator as well as intracorporeal colpotomy, which may increase the propensity of tumor dissemination (Ramirez et al., 2018). The feasibility, safety, and efficacy of robot-assisted SRH along with the patient's quality of life post-operation should be investigated in future studies of recurrent cervical cancer treatment to establish the optimal procedures for SRH and their standardization.

In conclusion, we have described the first case of recurrent cervical cancer successfully treated with robotic-assisted SRH.

With careful patient selection, robot-assisted SRH may represent an effective alternative to SRH via an open approach as a curative intervention for recurrent cervical cancer in a previously irradiated field.

### Ethical approval status

The Ethics Committee of Nara Medical University decided that this case report does not require IRB approval due to the nature of this study: a report describing the treatment of a single patient and thus does not meet the definition of human subjects research.

### CRediT authorship contribution statement

**Seiji Mabuchi:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Keita Waki:** Conceptualization, Data curation, Visualization.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2021.100882>.

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