

# Endometrial cancer with tubal metastasis detected during laparoscopic surgery in a patient undergoing fertility-sparing treatment with medroxyprogesterone acetate: a case report and review of the literature

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DOI: [10.31083/j.ejgo.2021.03.2334](https://doi.org/10.31083/j.ejgo.2021.03.2334)

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Submitted: 1 December 2020 Revised: 15 February 2021 Accepted: 22 February 2021 Published: 15 June 2021

**Objectives:** Medroxyprogesterone acetate (MPA) therapy is useful as a fertility-sparing treatment for early endometrial cancer, but it poses a risk of progression and recurrence during the treatment. We report a case of endometrial cancer with tubal metastases after long-term MPA therapy and review the literatures focusing on the failure of fertility-sparing treatment. **Case:** A nulliparous, 40 years old woman was started on MPA therapy after being diagnosed with grade 1 endometrioid carcinoma confined to the endometrium. She achieved complete remission after 10 months of treatment, but no pregnancy was established by assisted reproductive technology (ART). Eleven months after the first MPA therapy ended, atypical endometrial hyperplasia was confirmed. The disease was in remission again after the second MPA therapy for 8 months. The patient did not become pregnant by subsequent ART. Finally, a total laparoscopic hysterectomy with bilateral salpingo-oophorectomy was performed. The gross pathological specimen revealed a 13 mm mass near the left uterine cornu. Histopathology showed a left tube metastasis. She was diagnosed with FIGO stage IIIA endometrial cancer and underwent the staging surgery by laparotomy. After the second surgery, adjuvant chemotherapy was initiated. After 13 months of disease-free survival, a recurrence was histologically detected at the vaginal stump. Following intracavitary radiation therapy, there was no evidence of disease for 10 months. **Conclusions:** The patient undergoing fertility-sparing treatment should be apprised of a risk of life-threatening progression of the disease. Once the patient has opted out of fertility preservation, definitive hysterectomy should be strongly recommended.

## Keywords

Endometrial cancer; Fertility-sparing treatment; Laparoscopic surgery; Tubal metastasis; Vaginal stump recurrence

## 1. Introduction

Endometrial cancer is the most common gynecologic cancer in developed countries [1]. In Japan, cases have been increasing in recent years, with 9673 cases reported in 2014 [2]. Although it presents most frequently in postmenopausal women, up to 7% of cases occur in patients younger than 45 years [3]. Fertility preservation is an important quality-of-life issue in these younger patients, but it poses a risk of pro-

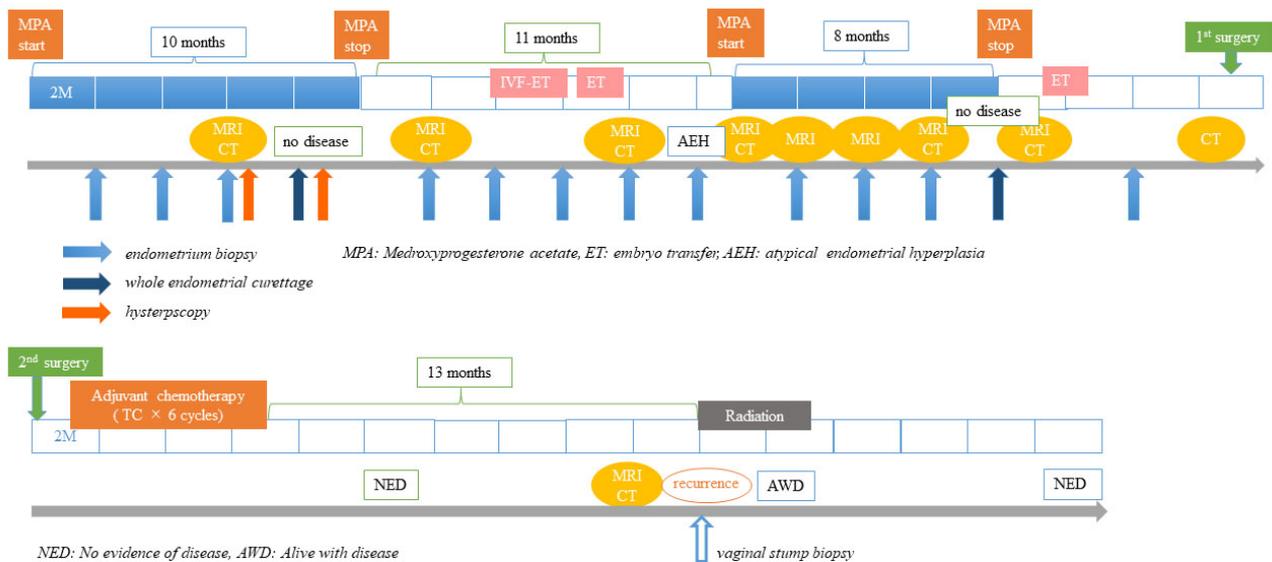
gression of the disease. Fertility-sparing treatment with progestin is useful for atypical endometrial hyperplasia (AEH) and early-stage, well-differentiated endometrioid carcinoma confined to the endometrium [4]. For patients undergoing fertility-preserving treatment, medroxyprogesterone acetate (MPA) 400–600 mg/day is the recommended therapy [5].

We report a case of endometrial cancer with tubal metastasis detected during laparoscopic surgery after the remission induced by repeated fertility-sparing treatments and review the literatures focusing on the failure of fertility-sparing treatment.

## 2. Case report

The patient was a nulliparous woman with no previous significant medical history. At the age of 40, after being diagnosed with grade 1 endometrioid carcinoma, she was started on MPA therapy. Before the treatment, MRI findings showed an endometrial tumor without myometrial invasion. The details of the clinical history are shown in Fig. 1. During the initial treatment over 10 months, she achieved complete remission based on MRI findings and histological findings by whole endometrial curettage. After that, she underwent assisted reproductive technology (ART) including oocyte pick up with GnRH agonist short protocol and natural cycle frozen embryo transfer, but no pregnancy was established. Eleven months after the first MPA therapy ended, AEH was confirmed by pipelle endometrial biopsy, indicating that her disease had recurred. She resumed MPA therapy after receiving an explanation about its risk. After 8 months of treatment, the endometrial cancer was in remission again. ART was performed once more, but she did not become pregnant. Finally, the patient decided to stop fertility treatments at the age of 43.

Five months from the end of the second MPA course, given the risk of intrauterine recurrence, total laparoscopic hysterectomy with bilateral salpingo-oophorectomy (TL-HBSO) was planned. Before the surgery, transvaginal ultrasonography findings showed an endometrial thickness of 4.2



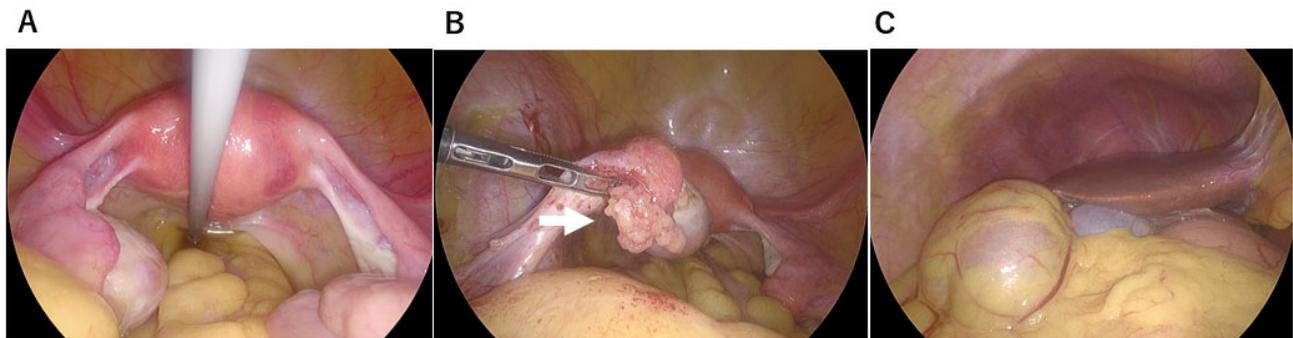
**Fig. 1. Clinical course.** AEH, atypical endometrial hyperplasia; AWD, alive with disease; ET, embryo transfer; IVF, *in vitro* fertilization; MPA, medroxyprogesterone acetate; NED, no evidence of disease; TC, paclitaxel (180 mg/m<sup>2</sup>) + carboplatin (AUC 6).



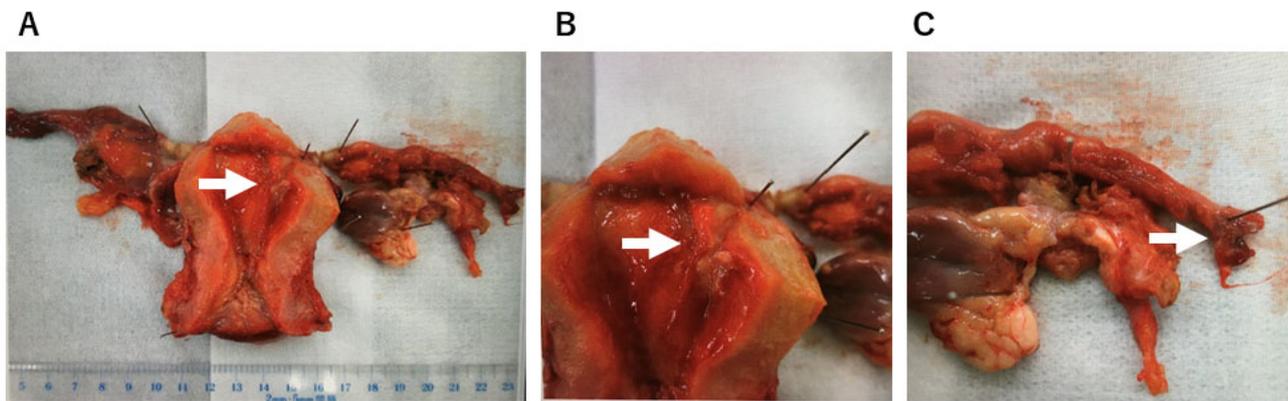
**Fig. 2. Findings on transvaginal ultrasonography and MRI before first surgery.** (A) Transvaginal ultrasonography. The endometrial thickness was 4 mm and the ovaries were normal in appearance. (B) T2-weighted sagittal image of MRI. (1) Before MPA therapy, there was a 13 mm endometrial tumor. (2) After the first MPA therapy, the endometrial tumor had resolved. (3) Before the first surgery, no tumor was found in the uterus.

mm and normal ovaries (Fig. 2). We confirmed no tumor in the uterus and no extrauterine lesions in the pelvis using MRI (Fig. 2). There was no evidence of metastasis on contrast-enhanced CT findings. During laparoscopic surgery, we found a small lesion on the left fimbria (Fig. 3). The uterus and the ovaries appeared normal. No visible metastases were found in the abdominal cavity. The surgery was performed without intraoperative pathological diagnosis. Macroscopic findings of the surgical specimen showed a mass near the left uterine cornu and normal-appearing Fallopian tubes. The histopathological findings included a 13 mm flat tumor, grade 1 endometrioid carcinoma involving the uterine corpus. There was no myometrial invasion and no lymphovascular invasion. The findings on the Fallopian tubes showed grade 1 endometrioid carcinoma (Figs. 4,5). The peritoneal

washing cytology was positive. The patient was diagnosed with advanced endometrial cancer, although we had considered the disease to be in remission after the second MPA therapy. A month after the first surgery, staging surgery by laparotomy, including retroperitoneal lymphadenectomy and omentectomy, was performed. The histopathological findings showed no metastases in the specimen. The postoperative diagnosis was FIGO stage IIIA endometrial cancer (pT3aN0M0). After the second surgery, six cycles of tri-weekly TC therapy (paclitaxel: 180 mg/m<sup>2</sup> + carboplatin: area under the curve = 6) were added as adjuvant chemotherapy. After 13 months of disease-free survival, a recurrence was histologically detected at the vaginal stump by the biopsy. After 24-Gy intracavitary radiation therapy, the patient has no evidence of disease for 10 months follow-up period.



**Fig. 3. Laparoscopic findings during the first surgery.** (A) The uterus and the ovaries were normal. (B) There was a small mass on the left fimbria. (C) No metastases were found in the abdominal cavity.



**Fig. 4. The specimen from the first surgery.** (A,B) There was a 13 mm mass near the left oviductal orifice. (C) The left fimbrial mass was not visible to the naked eye.

### 3. Discussion

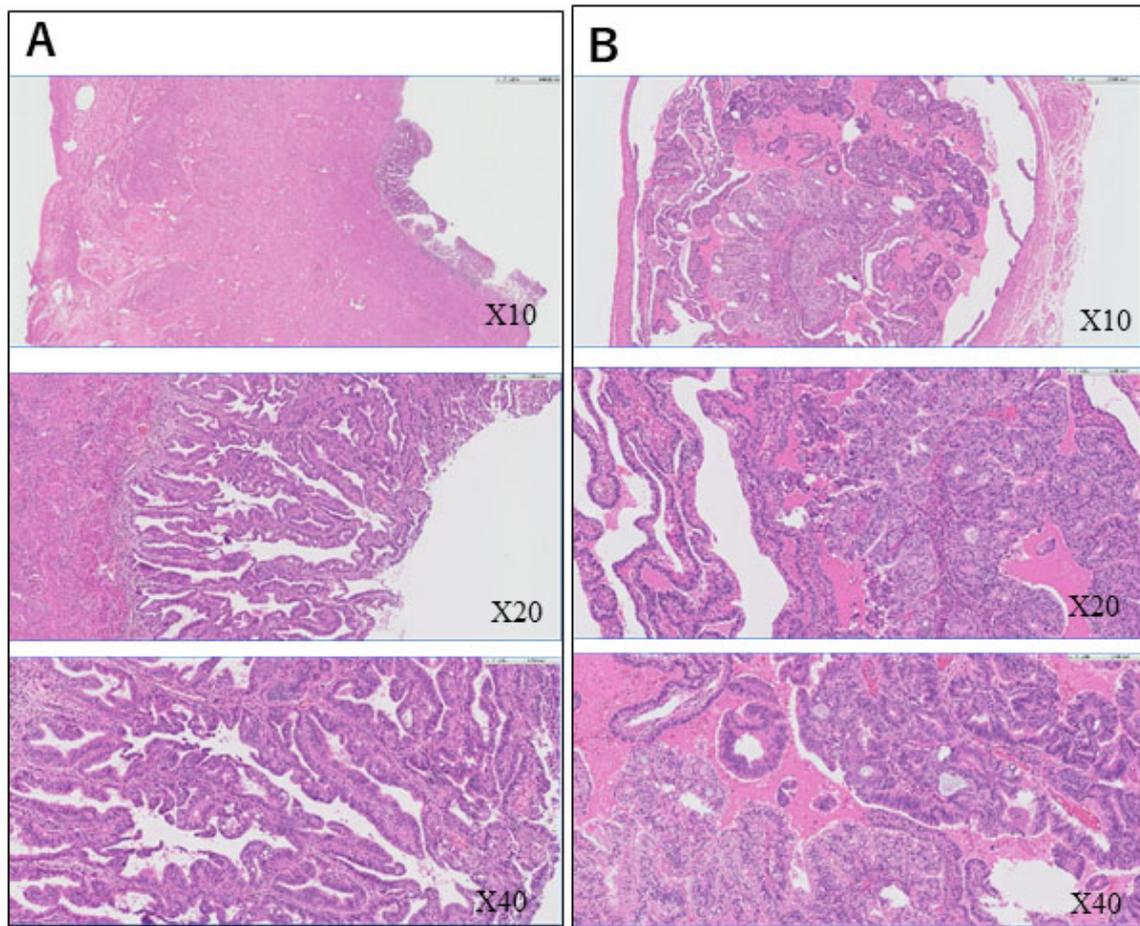
Current fertility-sparing treatment modalities include hormonal therapies involving oral progestins, progestin-releasing intrauterine devices, natural progesterone, oral contraceptives, selective estrogen receptor modulators, gonadotropin-releasing hormone agonist, and aromatase inhibitors [6]. Previous reports on progestin therapy for endometrial cancer revealed a high remission rate, but also a high relapse rate after remission (Table 1) (Ref. [4, 7–14]). In a meta-analysis of 408 cases with endometrial cancer, in which various types of fertility-sparing treatment were included and the patients treated were not limited to grade 1 endometrioid carcinoma confined to the endometrium, the fertility-sparing treatment achieved a remission rate of 76.2% and a relapse rate of 40.6% [7]. Another meta-analysis of 445 patients with presumed stage IA, well-differentiated endometrial cancer without myometrial invasion showed a remission rate of 82.4% and a relapse rate of 25.0% [8]. Gunderson *et al.* [4] reported that initial response induced by progestin therapy was observed in 74.6% of 280 patients with endometrial cancer and the rate of recurrence after initial remission was 35.4%.

MPA is commonly used as a fertility-sparing treatment of patients with well-differentiated endometrial cancer without

myometrial invasion, particularly in Japan. Japanese studies regarding high dose MPA therapy reported a relapse incidence range of 22.0%–66.7% (Table 2) (Ref. [15–21]). A recent meta-analysis on MPA therapy revealed the pooled relapse rate was 33% (95% confidence interval, 18%–53%), although the patients with atypical endometrial hyperplasia were included in this study [22].

Levonorgestrel-releasing intrauterine device (LNG-IUD) has been used as a fertility-sparing treatment in recent years. According to a review, 17 of 37 patients with stage IA without myometrial invasion, grade 1 endometrial cancer achieved complete response rate of 46% (95% confidence interval, 29%–63%) [23]. Several studies reported the outcomes of the combination of progestin releasing IUD with oral progestin to achieve better outcomes than either agent alone [24–27]. Kim *et al.* [24] conducted a prospective study of patients with stage IA, grade 1 endometrial cancer confined to the endometrium who were treated with progestin-releasing IUD plus oral progestin. Out of 16 patients, 14 (87.0%) achieved complete response and only 2 (14.3%) had recurrent disease.

Progestin therapy has been performed in combination with medication and surgical regimes. Hysteroscopy provides direct visualization of the endometrial cavity thereby allowing a targeted biopsy or excision of the lesions iden-



**Fig. 5. Histopathological findings of the uterus and the left Fallopian tube.** (A) The findings of the uterine corpus; grade 1 endometrioid carcinoma, a 13 mm tumor without myometrial or lymphovascular invasion. (B) The findings of the left Fallopian tube: grade 1 endometrioid carcinoma.

**Table 1. Literatures of fertility sparing treatment for endometrial cancer.**

Author (Year)	Design	Patients	Interventions	Remission n (%)	Relapse n (%)
Gallos (2012) [7]	Meta-analysis	I-II (G1-3)	FST	301/408 (76.2)	89/267 (40.6)
Qin (2016) [8]	Meta-analysis	IA (G1)	Oral progestin	367/445 (82.4)	92/367 (25.0)
Gunderson (2012) [4]	Review	IA (G1)	Progestin	209/280 (74.6)	74/209 (35.4)
Peiretti (2019) [9]	Review	IA (G1)	FST	228/299 (76.0)	77/228 (34.0)
Park (2013) [10]	Retrospective	IA (G1)	Oral progestin	115/148 (77.7)	35/115 (30.4)
Wang (2018) [11]	Retrospective	IA (G1)	FST	161/170 (94.7)	41/113 (36.3)
Yang (2019) [12]	Retrospective	IA (G1)	HSR + Progestine	36/37 (97.3)	4/36 (11.1)
Giampaolino (2019) [13]	Retrospective	IA (G1)	HSR + LNG-IUD	11/14 (78.6)	2/11 (18.2)
Mitsuhashi (2019) [14]	Retrospective	IA (G1)	Metformin + MPA	40/42 (95.0)	7/40 (17.5)

I-II, FIGO stage I-II; IA, FIGO stage IA without myometrium invasion; G, grade of endometrioid carcinoma; FST, fertility sparing treatment; MPA, medroxyprogesterone acetate; HSR, Hysteroscopic resection; LNG-IUD, levonorgestrel-intrauterine device.

tified during the procedure [28]. Hysteroscopic resection combined with progestin therapy may improve the result of fertility-sparing treatment for endometrial cancer patients. Yang *et al.* [12] reported the efficacy of hysteroscopic resection combined with progestin therapy in endometrial cancer patients. The patients had a remission rate and a relapse rate of 97.3% and 11.1%, respectively. The combination of hysteroscopic resection with LNG-IUD was also used as a

fertility-sparing treatment of patients with endometrial cancer. Giampaolino *et al.* [13] showed a complete response rate of 78.6% and a relapse rate of 18.2%.

In addition, several reports confirmed the effects of metformin, which is a biguanide widely prescribed for the treatment of type 2 diabetes mellitus [29]. Mitsuhashi *et al.* [30] conducted phase II study of MPA plus metformin as a fertility-sparing treatment option for patients with endome-

**Table 2. Japanese literatures of MPA therapy for endometrial cancer.**

Author (Year)	Design	Patients	Interventions	Remission n (%)	Relapse n (%)
Kaku (2001) [15]	Retrospective	IA G1-2	MPA 200-800 mg/day	9/12 (75.0)	2/9 (22.0)
Imai (2001) [16]	Retrospective	I-II G1-2	MPA 400-800 mg/day	8/14 (57.1)	3/8 (37.5)
Ota (2005) [17]	Retrospective	IA G1	MPA 600 mg/day	5/12 (42.0)	2/5 (40.0)
Niwa (2005) [18]	Prospective	IA G1	MPA 400-600 mg/day	12/12 (100)	8/12 (66.7)
Ushijima (2007) [19]	Prospective	IA G1	MPA 600 mg/day	14/22 (64.0)	8/14 (57.0)
Yamazawa (2007) [20]	Prospective	IA G1	MPA 400 mg/day	7/9 (78.0)	2/7 (22.0)
Minaguchi (2007) [21]	Prospective	IA G1	MPA 400-600 mg/day	14/18 (77.8)	5/14 (35.7)
Total				69/99 (69.7)	30/69 (43.5)

IA, FIGO stage IA without myometrium invasion; I-II, FIGO stage I-II; G, grade of endometrioid carcinoma; MPA, medroxyprogesterone acetate.

trial cancer and reported long-term outcomes following the trial. Of 42 patients with endometrial cancer, 40 (95.0%) achieved complete response and 7 (17.5%) of the 40 patients relapsed. To date, many clinical trials of fertility-sparing treatment of endometrial cancer using the various types of combination therapy are underway [14].

After a complete remission, the patients wishing to conceive should be advised to pursue pregnancy earlier and consider ART to improve pregnant rate [31]. The benefits of pregnancy on oncologic outcomes were reported by some literatures [32, 33]. Ichinose *et al.* [34] found that all patients who had receiving ART had a live birth and a low risk of recurrence compared to those who did not achieve pregnancy. Because of the high failure rate of hormonal treatment, it is currently recommended that a total hysterectomy is performed after completion of childbearing [31].

If a patient with recurrence after an initial treatment strongly desires the preservation of fertility, retreatment with progestin can be considered, but only under strict control [35]. Park *et al.* [10] showed a complete response rate of 85% and a recurrence rate of 18% to progestin re-treatment. In this report, the complete response rate to progestin re-treatment is reported to range from 50% to 100% for recurrent disease. In the 2-4% of patients who undergo repeated MPA treatment for intrauterine recurrence, there is a risk of progression of cancer stage [36]. In our case, although the patient was diagnosed with complete remission after the second MPA therapy for intrauterine recurrence after the initial treatment, the recurrent intrauterine disease developed in the fallopian tubes.

Standard surgical treatment results in excellent oncologic outcomes, particularly for patients with presumed low-risk endometrial cancer. However, fertility-sparing treatment delays definitive treatment with a hysterectomy and poses a risk of life-threatening progression of the disease. Ruiz *et al.* [37] reported that women treated with hormonal treatment are 92% (HR = 1.92; 95% confidence interval, 1.15-3.19) more likely to die compared to patients undergoing primary hysterectomy.

There are few reports focusing on the disease progression after fertility-sparing treatment for presumed stage IA, well-

differentiated endometrial cancer without myometrial invasion. Kaku *et al.* [15] reported that 2 of 9 responders with endometrial cancer developed relapse after MPA therapy and one of them had metastasis to the left obturator lymph node. The retrospective study of Ota *et al.* [17] showed that 8 patients received hysterectomy after MPA therapy and one of them died of the metastasis to the liver and the brain. The Gynecologic Oncology Group study evaluating the surgical pathologic features of 621 patients with stage I endometrial cancer showed that an appreciable number of patients (22%) have disease outside the uterus (lymph node metastasis, adnexal involvement, intraperitoneal spread and/or malignant cells in peritoneal washings). The adnexal involvement was detected in 5% of patients in the study [38]. A multicenter phase II study carried out at 16 institutions in Japan showed that one patient developing peritoneal carcinomatosis after repeated MPA therapy died of disease 4 months after staging surgery by laparotomy. The disease was speculated as synchronous malignancies of both endometrial and peritoneal carcinomas because there was no intrauterine recurrence 3 months before the development of the peritoneal lesions [19]. Synchronous ovarian cancer is seen in 5% of patients with endometrial cancer [39-41]. Several studies reported that synchronous ovarian cancer was detected in patients received hysterectomy after fertility-sparing treatment [19, 20].

To prevent a life-threatening progression of the disease after fertility-sparing treatment, it is important to select the appropriate candidates for the treatment. Selection of the appropriate candidates for fertility-sparing treatment depends on accurate cancer staging and histologic characteristics. MRI is essential to confirm eligibility by excluding myometrial invasion and tumor extension beyond the uterine corpus [42]. Histologic characteristics must be obtained by whole endometrial curettage since this approach is more accurate than endometrial biopsy for the assessment of tumor grade [43]. Our case was presumed stage IA, low-risk endometrial cancer before the first MPA therapy using MRI, CT, and whole endometrial curettage with hysteroscopy. The remission induced by the two courses of MPA therapy was evaluated using MRI and whole endometrial curettage.

Hysteroscopy was also used during the first MPA therapy course. As for the second MPA therapy course, it was possible that we could not detect the recurrent disease by MRI and whole endometrial curettage without hysteroscopy, because the intrauterine lesion was near the left uterine cornu. We should have used hysteroscopy to detect intrauterine recurrence, albeit with a potential increased risk of peritoneal spread during hysteroscopy. In a recent meta-analysis, although preoperative hysteroscopy resulted in a significant increase of positive peritoneal cytology, no impact on prognosis was observed [44]. In the present case, it was also difficult to detect the disease progression to the fallopian tubes before the first surgery. The laparoscopic findings were useful to detect the small lesion of the left fimbria, although there were not any macroscopic abnormalities from the surgical specimen. We doubted that the clinical stage of her endometrial cancer was revised to a higher stage, but TLHBSO was performed without an intraoperative pathological diagnosis as scheduled. As a result, the present case was diagnosed as advanced stage endometrial cancer and the recurrence was detected after the standard curative treatment, staging surgery followed by adjuvant chemotherapy. It is possible that the use of laparoscopic surgery for advanced stage endometrial cancer may be associated with local recurrence. We should have confirmed the tubal metastasis by intraoperative pathological diagnosis and converted the laparoscopic surgery to the staging surgery by laparotomy. Before the surgery, the patient should have been informed about the risk of progression of her disease and accepted the possibility of conversion to staging surgery.

#### 4. Conclusions

We experienced a case of endometrial cancer with tubal metastasis detected during laparoscopic surgery after remission of the disease induced by repeated cycles of MPA therapy. As is well known, it is difficult to detect disease recurrence and progression during long-term MPA therapy. The patient undergoing fertility-sparing treatment should be apprised of a risk of life-threatening progression of the disease. Once the patient has opted out of fertility preservation, definitive surgery with curative intent should be strongly recommended as soon as possible.

#### Author contributions

ID designed the report and made the initial draft of the manuscript. YN and RK performed the research. TO, SK, and NS advised on deciding the treatment principles. All authors participated in constructing the manuscript and approved the final version.

#### Ethics approval and consent to participate

The Ethics Committee of St. Marianna University School of Medicine approved the study (Approved number: 4514). We obtained written informed consent from the patient according to the Declaration of Helsinki.

#### Acknowledgment

We gratefully acknowledge the work of past and present members of our department.

#### Funding

This research received no external funding.

#### Conflict of interest

The authors declare no conflict of interest.

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