Complete resection of an endometrial cancer lesion by hysteroscopic tumor resection combined with photodynamic diagnosis: a case report

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Summary

Introduction: Treatment for early endometrial cancer (EC) has been shifting to less invasive surgery, including several reports of hysteroscopic tumor resection. Complete tumor resection is desired in these treatments. Photodynamic diagnosis (PDD) is the technique to increase the complete resection rate by red fluorescence of the lesion and has improved the prognosis of cystoscopic tumor resection for early bladder cancer. In gynecology, we showed that hysteroscopic PDD has high sensitivity for EC. Here, we report a case of EC in which no residual malignant lesions were found pathologically in hysterectomy after hysteroscopic tumor resection with PDD. Case: The patient was 54 years old when she was diagnosed with atypical endometrial hyperplasia by endometrial biopsy, but suspected to have EC on magnetic resonance imaging. Hysteroscopic tumor resection was planned for the definitive diagnosis. PDD was used in hysteroscopic surgery after informed consent was obtained. Under hysteroscopy, a tumefactive lesion was found on the anterior wall of the uterine cavity to near the left oviductal orifice, and was PDD-positive. The PDD-positive lesion was resected completely under hysteroscopy. The hysteroscopic specimen was pathologically diagnosed as endometrioid carcinoma, grade 1. Laparoscopic hysterectomy and bilateral salpingo-oophorectomy were then performed, but no residual malignancy was found in resected specimens. There has been no recurrence at one year after surgery without no adjunct therapy. Conclusion: Complete resection of endometrial cancer was achieved by hysteroscopic tumor resection with PDD. This case suggests that hysteroscopic surgery may be a less invasive treatment option for early EC.

Key words: Endometrial cancer; Hysteroscopy; Photodynamic diagnosis; 5-aminolevurinic acid.

Introduction

Endometrial cancer (EC) is a common gynecological malignancy that develops frequently in perimenopausal women [1], cases of EC have shown a recent increase [2]. Surgical treatment including total hysterectomy is standard for EC, but young patients meeting several criteria, including low malignancy and no muscle invasion, can be undergone hormonal therapy and/or surgical lesion resection as fertility preserving therapy [3-5] and these treatments play a significant role in improving the quality of life of young EC patients [6]. In this situation, there are some reports in which patients with early EC or atypical endometrial hyperplasia (AEH), a precancerous lesion, who underwent tumor resection had no recurrence despite not undergoing total hysterectomy [7, 8]. In another study, 9 of 11 patients with EC who underwent hysterectomy after hysteroscopic endometrial resection had no residual cancer in hysterectomy specimens [9]. These findings suggest that it may be possible to perform uterine conservative therapy for early EC using hysteroscopic surgery.

Complete tumor resection is desired in hysteroscopic tumor resection for EC and AEH. In some clinical fields, photodynamic diagnosis (PDD) is used to increase the complete tumor resection rate. In bladder conservation therapy for early bladder cancer, lesions are resected with cystoscopic surgery. PDD has been combined with this surgery. A photosensitizer used in PDD, 5-aminolevurinic acid (5ALA), is metabolized to the heme precursor protoporphyrin IX (PpIX) in vivo. PpIX accumulates in tumors and emits red fluorescence at about 650 nm when irradiated with blue excitation light at 400 nm. PDD is used to identify tumors based on these properties. Minimal lesions and lesion borders can be identified by PDD clearly, leading to improved therapeutic outcomes for early bladder cancer [10, 11].

Hysteroscopic 5ALA-PDD has high sensitivity for lesion identification in EC and AEH, but 5ALA-PDD is not widely used in gynecology [12]. Use of 5ALA-PDD may permit easy identification of minimal lesions and improve tumor resection rates in hysteroscopic surgery for EC and AEH. Here, we report the case of a patient who underwent hysteroscopic tumor resection with 5ALA-PDD that achieved complete resection of endomyometrial lesions.

Case Presentation

The patient was a 54-year-old woman with gravida 2 para 1, menopause at age 51 years and body mass index
Complete resection of an endometrial cancer lesion was performed under hysteroscopy in the patient. This case suggests that hysteroscopic tumor resection can be a radical cure for EC. Vios et al. presented a case of EC treated in which the patient refused additive therapy, including total hysterectomy or hormone therapy, after hysteroscopic tumor resection, and was then followed up and had no recurrence of EC for 5 years [7]. Casadio et al. also found no recurrence at 5 years after treatment in 9 patients who underwent hysteroscopic tumor resection and combined treatment with a levonorgestrel-releasing intrauterine de-
vice (LNG-IUD), due to surgical intolerance preventing a radical operation [13].

Surgical treatment of early EC has become less invasive in moving from laparotomy to laparoscopic surgery and robot-assisted surgery [14]. However, patients with severe obesity frequently have postoperative complications, despite minimally invasive surgical procedures, and there is a need to improve outcomes in patients at high risk for perioperative complications [15]. Hysteroscopic surgery is less invasive than laparoscopic surgery, and may be useful for these patients. There are only a few case reports of early EC treated by hysteroscopic tumor resection, but these reports show its utility and feasibility. Therefore, further studies should be conducted, including assessment of radical therapy.

There are also reports that show possible difficulties in complete tumor resection by hysteroscopic surgery. Though hysteroscopic operation can detect and remove more lesions than D&C [16], in patients who underwent hysteroscopic polypectomy and were shown to have EC and AEH based on polyp specimens, Elyashiv et al. found residual lesions in 91.2% of cases, including in regions other than resected polyp roots [17]. Vilos et al. also detected residual lesions in hysterectomy specimens in 6 of 8 patients with EC who underwent partial hysteroscopic endomyometrial resection [9]. The commonality in patients with residual EC lesions after hysteroscopic tumor resection was that complete endometrial resection was not performed. Under hysteroscopic observation, identifying small lesions is difficult, particularly under poor endometrial conditions. To facilitate hysteroscopic tumor resection as curative treatment for EC, total endometrial resection should be the basic procedure, rather than selective lesion resection.

Though total endometrial resection is advantageous for complete cure of EC, it damages endometrium severely.
Figure 3. — Pathological findings in a specimen resected under hysteroscopy (hematoxylin-eosin stain, A: ×40, B: ×400). Atypical endometrial glands with swollen nuclei proliferated as back-to-back structures. Flat hyperplasia of these glands showing complicated divergence (A). Overgrowth of the glands with accumulated nuclei was also found (B). Based on these results, the diagnosis was endometrioid carcinoma grade 1.

Figure 4. — Macroscopic and microscopic findings in hysterectomy specimens. (A): Macroscopic findings in the uterus. (B): Gross findings around the left oviductal orifice, in which a lesion was observed hysteroscopically. (C): Microscopic findings in the uterus (hematoxylin-eosin stain). No gross definite residual tumor was found in the removed uterus (A, B). Pathological examination showed no definite hyperplasia of atypical endometrial ducts and no residual tumor cells.

Though there are few previous reports which show the negative effect of the total endometrial resection on pregnancy, as Inoue et al. showed the negative effect of endometrium damage due to the D&C on pregnancy [3], a procedure for complete resection of lesions only may be required to improve the outcome of fertility preservation therapy. For young patients with early-stage EC and AEH who desire to preserve their fertility, LNG-IUD implantation is performed as a minimal invasive treatment [18], but Giampaolino et al. reported that hysteroscopic tumor resection along with the LNG-IUD reduced the recurrence rate [4]. In hysteroscopic 5ALA-PDD, lesions show red fluorescence under irradiation with blue excitation light, which allows easy identification. In our case, total endometrial resection was not performed, but the lesion was completely resected using this procedure. This case suggests that 5ALA-PDD-assisted hysteroscopic surgery reduces residual tumor and permits complete resection. Thus,
5ALA-PDD may be useful for patients who require as much lesion resection as possible, but also require fertility preservation through minimal invasion.

Our previous study showed that 5ALA-PDD has sensitivity of 93.8% for identification of EC and AEH [12]. This sensitivity is superior to that of skilled gynecologists using hysteroscopy (86.6%) [19]; therefore, 5ALA-PDD is an extremely sensitive technique. Furthermore, 5ALA-PDD contributes to identification of minimal lesions in hysteroscopy. We identified minimal AEH lesions using 5ALA-PDD alone to determine the therapeutic policy [20]. Partial hysteroscopic tumor resection combined with hormone therapy using megestrol acetate and medroxyprogesterone acetate achieves high remission rates [21-25], and combination of hysteroscopic 5ALA-PDD with this therapy may further improve treatment outcomes for fertility preservation.

There are several remaining concerns with use of hysteroscopic tumor resection and 5ALA-PDD for patients with EC. The first issue is the effect of thermal denaturation of sampling lesions during hysteroscopy. In hysteroscopic surgery, lesions are resected with a loop electrode of a resectoscope, which makes it difficult to assess myometrial invasion, an important prognostic factor for EC, which may underestimate recurrence risks. A second issue is the concern of intraperitoneal dissemination of tumor cells via the oviduct in patients with malignancy in the uterine cavity because hysteroscopic surgery is performed with the uterine cavity filled with perfusate. Ascetic cytology was negative in our patient, but Chang et al. conducted a meta-analysis of hysteroscopy for EC and showed significantly higher positive rates for ascetic cytology in patients who underwent hysteroscopy [26]. However, it is unclear whether hysteroscopy itself causes intraperitoneal dissemination of tumor cells. Patients with early cancer have no significant difference in positive rates for ascetic cytology after hysteroscopy, and hysteroscopy is not a significant factor for long-term prognosis [26]. However, risks for intraperitoneal dissemination of tumor cells with use of a hysteroscope require ongoing assessment. Finally, 5ALA-PDD has high sensitivity for identification of endometrial lesions, but has low specificity [12]. This is not a concern in a case in which fertility is unimportant, but excessive invasion of the endometrium due to low specificity is a problem for fertility preservation. Thus, further improvements are needed to increase the specificity of 5ALA-PDD.

**Conclusions**

We report a case of complete resection of endometrial cancer by 5ALA-PDD combined with hysteroscopic tumor resection. This case suggests that hysteroscopic surgery may be a less invasive treatment option for early endometrial cancer. This method still has some concerns, but further studies are likely to resolve these issues.

**Authors’ contributions**

YM designed the study, performed the operation, and wrote the manuscript. YM and KT obtained informed consent from the patient. KB designed the study. KT recruited the patient. KB, YK, IK, DA provided critical advice on the manuscript. All authors contributed to revisions of the text, and all authors read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

The subject gave her informed consent for inclusion before she participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and this procedure was approved by the Certified Review Board of Keio (approved on February 8, 2019; approval no. N20170318-1) and registered the Japan Registry of Clinical Trials (https://jRCTs031180123) and the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (https://www.umin.ac.jp/, registration no. UMIN000031637).

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**Conflict of Interest**

All authors have no financial relationships to disclose.

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