



# Long-term survival of a patient with stage IIIC2 grade 3 endometrioid endometrial carcinoma treated with surgery alone

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## ABSTRACT

**Background:** The therapeutic benefit of lymphadenectomy in endometrial carcinoma is controversial.

**Case:** A 70-year-old woman with grade 3 endometrioid endometrial carcinoma with deep myometrial invasion underwent surgical staging comprising total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and pelvic and *para*-aortic lymphadenectomy. Pathological examination revealed micro-metastases in the *para*-aortic node, pelvic node, and left ovary. Peritoneal cytology was negative, and abnormal p53 expression was not detected. The patient was diagnosed with stage IIIC2 endometrial carcinoma. Adjuvant chemotherapy was advised, but the patient refused chemotherapy and was followed up regularly thereafter. The patient survived without any evidence of disease 67 months after surgery.

**Conclusion:** Pelvic and *para*-aortic lymphadenectomy may have a therapeutic benefit in a patient with high-grade endometrioid carcinoma, but without p53 abnormality.

## 1. Introduction

Endometrial carcinoma is the most common gynecologic malignancy in developed countries (Morice et al., 2016). The cornerstone of treatment is surgery, comprising hysterectomy, bilateral salpingo-oophorectomy. Pelvic lymphadenectomy with or without *para*-aortic lymphadenectomy, is also performed in patients at risk for recurrence. Surgical staging including lymphadenectomy confers prognostic benefit to delineate the exact extent of the disease and to tailor adjuvant treatment. In contrast, the therapeutic benefit of lymphadenectomy remains controversial. The effects of surgery alone in improving prognosis cannot be evaluated in node-positive patients when they receive adjuvant radiotherapy and/or chemotherapy after surgery. Herein, we describe a case of grade 3 endometrioid endometrial carcinoma without p53 abnormality with *para*-aortic and pelvic lymph node metastasis who was treated with surgery alone and survived for more than 5 years after surgery without evidence of disease.

## 2. Case

A 70-year-old woman, gravida 1, para 1, presented with abnormal genital bleeding. Her body mass index was 18.7. Pelvic examination did not detect overt abnormalities other than uterine bleeding; however,

vaginal ultrasonography revealed an endometrial tumor. Endometrial sampling showed grade 3 endometrioid carcinoma. Pelvic magnetic resonance imaging showed an endometrial tumor with deep myometrial invasion (Fig. 1). An 18F-fluorodeoxyglucose positron emission tomography/computed tomography showed an abnormal uptake in the uterine cavity (maximal standardized uptake value of 19.8) but not in the extrauterine areas. The serum CA-125 level was 25 U/mL. Surgical staging, comprising total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and pelvic and *para*-aortic lymphadenectomy was performed. No peritoneal dissemination, ovarian tumor, or lymph node swelling was observed. Pathological examination showed a high-grade carcinoma, immunohistochemically positive for estrogen receptor and p53 (wild type) and negative for WT-1, consistent with grade 3 endometrioid carcinoma (Fig. 2A). Myometrial invasion to the outer third layer was observed, but cervical invasion or lymphovascular invasion was not observed. Peritoneal cytology was negative. However, microscopic metastasis ( $\leq 2$  mm in size) in the left ovary, a right obturator lymph node, and a right *para*-aortic lymph node were identified using conventional histological technique (only one slice was taken from each single node) (Fig. 2B). The number of positive lymph nodes included one of the eight pelvic nodes and one of the five *para*-aortic nodes that were removed. The patient was diagnosed with International Federation of Gynecology and Obstetrics stage IIIC2,

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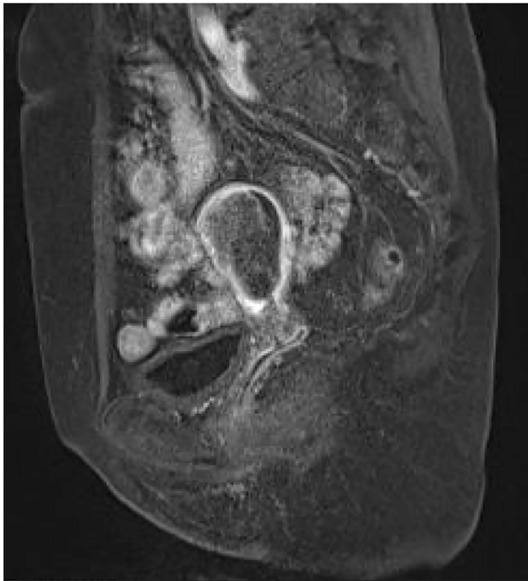
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**Fig. 1.** Saggital T1-weighted contrast-enhanced magnetic resonance imaging (after gadolinium administration) showing endometrial tumor with deep myometrial invasion.

PT3aN1M0, endometrial carcinoma. The postoperative course was uneventful. Adjuvant chemotherapy consisting of paclitaxel and carboplatin was offered, but the patient refused because the adverse effects associated with chemotherapy might decrease her quality of life. Thereafter, the patient was followed up regularly. At the time of writing of this report, the patient was alive without evidence of disease or lower-extremity lymphedema 67 months after surgery.

### 3. Discussion

The present case indicates that surgical removal of positive lymph nodes had a therapeutic benefit in a patient with micrometastatic lesions that could be removed surgically. A previous study has shown that five-year overall survival was 40% for patients with endometrial cancer with positive lymph nodes who were treated with surgery alone (Brown et al., 2013). However, whether a patient with grade 3 endometrioid carcinoma with *para*-aortic node metastasis survived for a long period was not reported in that study. Pelvic lymphadenectomy alone in patients with endometrial carcinoma, most of whom had low-risk diseases, has not been shown to improve survival in randomized controlled trials (Kitchener et al., 2009). In contrast, combined pelvic and *para*-aortic lymphadenectomy appears to improve survival in patients with intermediate- or high-risk diseases (Todo et al., 2010). *Para*-aortic node metastasis is observed in approximately half of the patients with pelvic

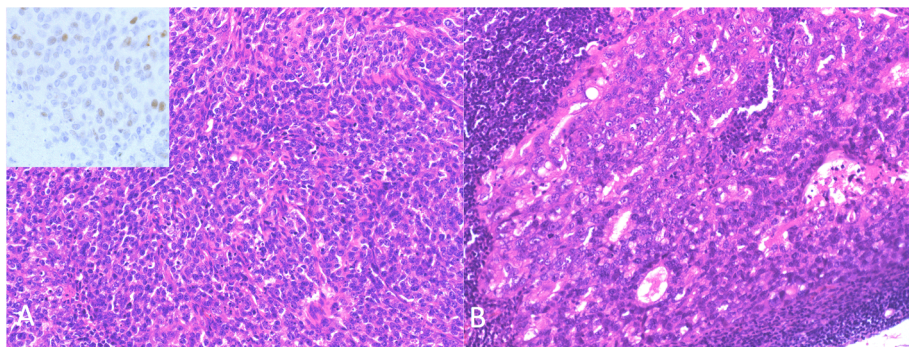
node metastasis (Mariani et al., 2004) and deep myometrial invasion is a risk factor for *para*-aortic node metastasis (Morrow et al., 1991). The rate of *para*-aortic node recurrence was significantly higher in patients who underwent pelvic lymphadenectomy alone than in patients who underwent both pelvic and *para*-aortic lymphadenectomy (Todo et al., 2011). Thus, *para*-aortic node metastasis left after pelvic lymphadenectomy may develop recurrent lesions and ultimately reduce the chances of patients' survival.

Systematic lymphadenectomy can remove all metastatic lymph nodes, as suggested by the observation that lymph node recurrence in the regions where lymphadenectomy was performed is very rare (Todo et al., 2011; Otsuka et al., 2002). Although chemotherapy is more effective in the adjuvant setting in advanced endometrial carcinoma compared to irradiation (Randall et al., 2006), current chemotherapy may not be effective in grade 3 endometrioid carcinoma (Fujimoto et al., 2009). Poor prognosis associated with grade 3 tumors may partly be caused by micro-metastasis left after surgery when systematic lymphadenectomy is not performed.

Sentinel lymph node mapping is a useful method to detect lymph node metastasis when ultra-staging, combining serial sectioning and immunohistochemical analysis, is performed (Rossi et al., 2017). However, ultra-staging may be difficult to perform during surgery. In addition, all the metastatic lymph nodes may not be mapped. Lymph node biopsy alone without systematic lymphadenectomy may leave undetected lymph node metastases that are not eradicated by adjuvant therapy.

Despite a high-grade tumor and older age, both of which are well-known poor prognostic factors in endometrial carcinoma (Morice et al., 2016), the present case had a favorable long-term survival. Several possible explanations can be proposed. First, only micro-metastasis was observed at all metastatic sites. Adjuvant therapy may not be necessary for low-volume lymph node metastasis, including micro-metastasis, which may be missed without serial sectioning. Second, the number of positive nodes was only two. In a previous report on patients who underwent systematic pelvic and *para*-aortic lymphadenectomy followed by platinum-based chemotherapy, metastasis in one or two lymph nodes was shown to have little effect on survival irrespective of *para*-aortic node involvement (Sueoka et al., 2015). Third, peritoneal cytology, which may be a risk factor for recurrence, was negative. Lastly, abnormal p53 expression (overexpression or null expression), which is associated with poor outcome in grade 3 endometrioid endometrial carcinomas (Bosse et al., 2018), was not observed. In endometrioid ovarian carcinoma, *TP53* mutation is associated with high genomic complexity, advanced stage disease, incomplete debulking and inferior survival (Hollis et al., 2020).

We performed an open surgery in this patient, because it was necessary for our surgical team to completely dissect the pelvic and *para*-aortic lymph nodes. Furthermore, the noninferiority of laparoscopy versus laparotomy for recurrence after surgical staging in endometrial



**Fig. 2.** A. Endometrial tumor: a grade 3 endometrioid carcinoma consisting of more than 50% of solid component; Inset. p53 immunohistochemistry showing wild-type staining pattern. B. *Para*-aortic lymph node metastasis (micrometastasis).

carcinoma was not established at the time of surgery (Walker et al., 2012).

In conclusion, systematic pelvic and *para*-aortic lymphadenectomy may have a therapeutic benefit in a patient with high-grade endometrioid carcinoma, but without p53 abnormality. As the effects of adjuvant therapies to eradicate residual metastasis in lymph nodes are uncertain, we believe that surgical staging, including *para*-aortic lymphadenectomy, should be performed in patients with deep myometrial invasion and/or high-grade endometrioid carcinoma until more accurate pre- and/or intraoperative detection methods for lymph node metastasis are developed.

#### 4. Consent

Informed consent was obtained from the patient for publication of this report and accompanying images.

#### CRedit authorship contribution statement

**Isao Otsuka:** Conceptualization, Data curation, Writing – original draft. **Mizuho Kadooka:** Data curation, Writing – review & editing. **Takuto Matsuura:** Writing – review & editing.

#### 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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