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# Pathological factors associated with omental metastases in endometrial cancer

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**Summary**

*Purpose of investigation:* This study aimed to assess the role of omentectomy in the surgical therapy of endometrial cancer. *Materials and Methods:* A retrospective study was performed in 98 patients who were pathologically diagnosed with endometrial cancer and had initially undergone surgical therapy at the present institution. This study analyzed the relationship between omental metastasis and clinicopathological factors. *Results:* Omental metastasis was detected in nine patients (9%). On univariate analysis, significant number of omental metastatic lesions were detected in few cases by positive peritoneal cytology, adnexal metastasis, gross dissemination, and lymphovascular space involvement. On multivariate analysis, adnexal metastasis were a significant risk factor. The sensitivity of the special histological type and the specificity of the macroscopic peritoneal dissemination and adnexal metastasis were all high. *Conclusion:* Omentectomy plays a significant role in determining the exact surgical staging in cases with non-endometrioid cancer, adnexal metastasis, and macroscopic peritoneal dissemination.

*Key words:* Endometrial cancer; Omentectomy; Omental metastasis; Pathological factor; Uterine cancer.

## Introduction

Endometrial cancer is a malignant tumor, the incidence of which is increasing in Japan because of the growth in the population of nulliparous females, attributed to delayed marriages and lifestyle changes. The initial management of endometrial cancer includes surgery, and the standard surgical procedure is hysterectomy with bilateral salpingo-oophorectomy [1] and retroperitoneal lymphadenectomy/ biopsy (pelvic and paraaortic lymph nodes). The present authors frequently change surgical procedures depending on the histological type of the tumor or the presence of extrauterine metastasis or myometrial invasion.

Risk factors for recurrence are deep myometrial invasion [2], endometrioid adenocarcinoma grade 3 (G3) [2, 3], non-endometrioid adenocarcinoma [4, 5], lymphovascular space invasion (LVSI) [4, 6], adnexal metastasis [7], cervical involvement [7, 8], lymph node metastasis, and distant metastasis; of these, the latter is a particularly important factor in recurrence and poor prognosis.

Accurate risk assessment is important for adequate postoperative therapy and the estimation of prognosis. Lymph node metastasis is often observed in patients with endometrial cancer, and biopsy or lymphadenectomy of regional lymph nodes is a reliable diagnostic indicator of extrauterine metastasis. Endometrial cancer spreads throughout the uterine tube, accompanied by organized peritoneal dissemination, the assessment of which is also important, depending on the histological type.

Peritoneal dissemination is diagnosed on the basis of macroscopic observations and peritoneal biopsy. The omentum is a lymphatic tissue comprised of many vessels and microvessels, and omentectomy may be useful in the evaluation of peritoneal dissemination.

According to the National Comprehensive Cancer Network (NCCN) guidelines [9], omentectomy is recommended in cases with increased CA-125 levels and following histological types: serous adenocarcinoma, clear cell adenocarcinoma, and carcinosarcoma. Furthermore, it is recommended in cases with suspicious extrauterine lesions according to magnetic resonance imaging (MRI) and computed tomography (CT). However, indications for omentectomy remain controversial [10].

In this report, the authors discuss pathological features in relation to confirming the role of omentectomy in the surgical therapy of endometrial cancer.

## Materials and Methods

Subjects included 98 patients who were pathologically diagnosed with endometrial cancer at the present institution and had initially undergone surgical therapy between 2007 and 2011 [including hysterectomy, bilateral salpingo-oophorectomy (BSO), and omentectomy]. Clinicopathological factors of these cases were retrospectively analyzed. At the present institution, endometrial biopsies or curettage were performed in cases with a definitive diagnosis of endometrial cancer. Moreover, pelvic MRIs, thoracoabdominal CTs, and hysteroscopies were performed

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Table 1. — *Patients' characteristics.*

| | | | Omental metastasis positive | Omental metastasis negative | *p*-value |
|---|---|---|---|---|---|
| Histological type | EM* | 66 | 1 | 65 | NS |
| | Non- EM* | 32 | 8 | 24 | |
| Peritoneal cytology | + | 19 | 9 | 10 | <0.001 |
| | – | 79 | 0 | 79 | |
| Adnexal metastasis | + | 16 | 6 | 10 | 0.001 |
| | – | 82 | 3 | 79 | |
| Myometrial invasion | 1/2< | 70 | 7 | 63 | NS |
| | 1/2≥ | 28 | 2 | 26 | |
| Cervical involvement | + | 24 | 4 | 20 | NS |
| | – | 74 | 5 | 69 | |
| LVSI** | + | 65 | 7 | 58 | 0.025 |
| | – | 33 | 2 | 31 | |
| Parametrium invasion | + | 4 | 3 | 1 | NS |
| | – | 94 | 6 | 88 | |
| Lymph node metastasis | + | 33 | 1 | 32 | NS |
| | – | 65 | 8 | 57 | |
| Macroscopic peritoneal dissemination | + | 7 | 7 | 0 | <0.001 |
| | – | 91 | 2 | 89 | |
| CA125(U/ml) | | | 268±497.1 | 71±109.3 | 0.006 |
| CA19-9(U/ml) | | | 125.4±132.0 | 31.0±55.7 | 0.002 |
| PFS*** (days) | | | 207.2±132.0 | 822.0±536.0 | 0.001 |

* endometrioid adenocarcinoma; ** lymphovascular space involvement; *** progression-free survival.

to evaluate the clinical stage; appropriate surgical procedures were then selected, including lymphadenectomy.

Hysterectomy encompasses simple hysterectomy, modified radical hysterectomy, and radical hysterectomy; the choice of procedure is determined on the basis of cervical stromal invasion and myometrial invasion. BSO was performed in all cases, whereas pelvic lymphadenectomy was performed in all cases except those with Stage IA and endometrioid adenocarcinoma G1 without myometrial invasion. Para-aortic lymphadenectomy was performed in following cases: pelvic lymph node metastasis, adnexal metastasis, myometrial invasion that involved at least one-half thickness, endometrioid adenocarcinoma G3, and non-endometrioid adenocarcinoma, including serous adenocarcinoma, clear cell adenocarcinoma, and carcinosarcoma. Omentecomy was performed in all cases where para-aortic lymphadenectomy was performed. Partial omentectomy was performed in principle, but subtotal omentectomy was performed in cases where macroscopic peritoneal dissemination was detected. In some cases with severe complications, retroperitoneal lymphadenectomy was not performed.

Intraoperative pathological diagnosis was achieved by the pathologist in most cases after evaluating the histological type, myometrial invasion, and distant metastasis; this determination assisted in determining the surgical technique to be employed for lymphadenectomy. Intraoperative peritoneal cytology was not performed at this institute.

Risk factors for recurrence were assessed on the basis of the pathological diagnosis. Postoperative multidrug adjuvant chemotherapy included platinum drugs, which was administered for three to six cycles in all cases with risk factors. The follow-up period was ten to 15 years following initial therapy, and follow-up examinations to check for recurrence included gynecological examinations, vaginal cytology, thoracoabdominal CTs, and the identification of tumor markers.

This study analyzed following pathological factors: histological type, peritoneal cytology, adnexal metastasis, myometrial invasion, LVSI, cervical stromal invasion, parametrial invasion, regional lymph node metastasis, and peritoneal dissemination.

This study was conducted with the approval from the ethics committee of the School of Medicine, Keio University (approval number: 20120243).

*Statistical analysis*

The SPSS software (version 20) was used for statistical analysis, which was performed using Fisher's exact test and Student's t-test. $P$ values < 0.05 were considered statistically significant. Kaplan–Meier curves were used to evaluate the progression-free survival and were compared using standard log-rank tests.

## Results

*Patient characteristics*

Patients' median age was 59 years (range: 34–77 years). Omentectomy was performed in all cases. Complications developing because of omentectomy were not clearly determined in any case. Pelvic and para-aortic lymphadenectomy were performed in most cases, but retroperitoneal lymphadenectomy were not performed in 7% cases. Patient characteristics and clinicopathological features of all 98 cases are presented in Table 1.

Sixty-six patients were diagnosed with endometrioid adenocarcinoma (19, 24, and 23 with grades 1, 2, and 3, respectively), 16 with serous adenocarcinoma, three with clear cell adenocarcinoma, ten with carcinosarcoma, and three with undifferentiated carcinoma. Omental metastasis was detected in 1.5% cases with endometrioid adenocarcinoma, 31.2% with serous adenocarcinoma, 33.3% with clear cell adenocarcinoma, and 20.0% with carcinosarcoma.

Table 2. — *Clinicopathological factors of the nine cases with omental metastasis.*

| No. | Age | Suspicious omental metastasis | | pTN | Histological type | MI | AM | LM | DM |
|---|---|---|---|---|---|---|---|---|---|
| | | Preoperative | Intraoperative | | | | | | |
| 1 | 56 | – | – | pT1AN0 | Serous | – | – | – | – |
| 2 | 64 | – | + | pT1BN1 | Serous | >1/2 | – | + | – |
| 3 | 68 | + | + | pT3BN0 | Serous | >1/2 | + | – | – |
| 4 | 62 | + | + | pT3AN0 | Serous | >1/2 | + | – | – |
| 5 | 56 | + | + | pT3AN0 | Serous | >1/2 | + | – | – |
| 6 | 70 | – | + | pT2N0 | Clear | >1/2 | – | – | – |
| 7 | 72 | – | – | pT3AN0 | Carcinosarcoma | >1/2 | + | – | – |
| 8 | 37 | + | + | pT3AN0 | Carcinosarcoma | <1/2 | + | – | – |
| 9 | 57 | – | + | pT3AN0 | EM G1 | >1/2 | + | – | – |

Preoperative: preoperative imaging (MRI, CT). Intraoperative: intraoperative macroscopic finding.
Serous: serous adenocarcinoma, clear: clear cell adenocarcinoma, EM: endometrial adenocarcinoma, MI: myometrial invasion, AM: adnexal metastasis, LM: lymph node metastasis, DM: distant metastasis.

Table 3. — *Univariate and multivariate analysis of pathological factors.*

| | | Univariate analysis (*p* value) | Multivariate analysis (*p* value) | Hazard ratio (95% CI) |
|---|---|---|---|---|
| Non-EM histological type | (VS EM) | 0.429 | NS | |
| Positive peritoneal cytology | (VS negative) | <0.001 | NS | |
| Adnexal metastasis | (VS negative) | 0.001 | 0.003 | 8.864 (2.062-38.108) |
| Myometrial invasion > 1/2 | (VS <1/2) | 0.052 | NS | |
| Cervical involvement | (VS negative) | 0.144 | NS | |
| Lymph node metastasis | (VS negative) | 0.524 | NS | |
| Peritoneal dissemination by inspection | (VS negative) | <0.001 | | |

Table 4. — *Sensitivity and specificity of pathological factors.*

| | | Sensitivity | Specificity |
|---|---|---|---|
| Non-EM histological type | (VS EM) | 88.9% | 47.2% |
| Adnexal metastasis | (VS negative) | 66.7% | 87.7% |
| Myometrial invasion > 1/2 | (VS <1/2) | 66.7% | 30.0% |
| Cervical involvement | (VS negative) | 44.4% | 77.5% |
| Lymph node metastasis | (VS negative) | 22.2% | 64.0% |
| Peritoneal dissemination by inspection | (VS negative) | 77.8% | 100.0% |

The following pathological factors revealed significant correlation with omental metastasis: positive peritoneal cytology, adnexal metastasis, LVSI, peritoneal dissemination, CA125, and CA19-9 levels. Patients without omental metastasis had a significantly better prognosis. The median follow-up period was 25 months (range: 2–60 months).

*Analysis of pathological factors in omental metastasis cases*

Pathological factors involved in omental metastasis cases are presented in Table 2. Omental metastasis was detected in nine of 98 cases (9%), including one case with endometrioid adenocarcinoma, five with serous adenocarcinomas, one with clear cell adenocarcinoma, and two with carcinosarcomas.

In seven of these nine cases, the macroscopic peritoneal dissemination was detected during surgery, along with four other cases wherein peritoneal dissemination had already been detected before surgery by either CT or MRI. Microscopic omental metastasis were detected in two cases: one with serous adenocarcinoma and another with carcinosarcoma; both these cases were subsequently diagnosed with serous adenocarcinoma with preoperative endometrial biopsy. In both cases, tumor markers were found at levels lower than cut-off values, with no omental metastasis identified by either CT or MRI, and with no omental involvement detected by intraoperative inspection and palpation. In all cases, peritoneal cytology was positive, and no metastasis was detected in other organs.

*Analysis of predictive factors of omental metastasis*

According to univariate analyses, the hazard of omental metastasis were significantly higher in the groups of positive peritoneal cytology, adnexal metastasis, and gross peritoneal dissemination (Table 3).

Histological type, myometrial invasion, and adnexal metastasis were diagnosed by aforementioned intraoperative pathological diagnosis. Among these pathological factors, multivariate analysis revealed that the presence of adnexal metastasis was a significant risk factor (Table 3).

Sensitivity and specificity are presented in Table 4. The sensitivity of the non-endometrioid carcinoma, peritoneal dissemination, adnexal metastasis, and myometrial inva-

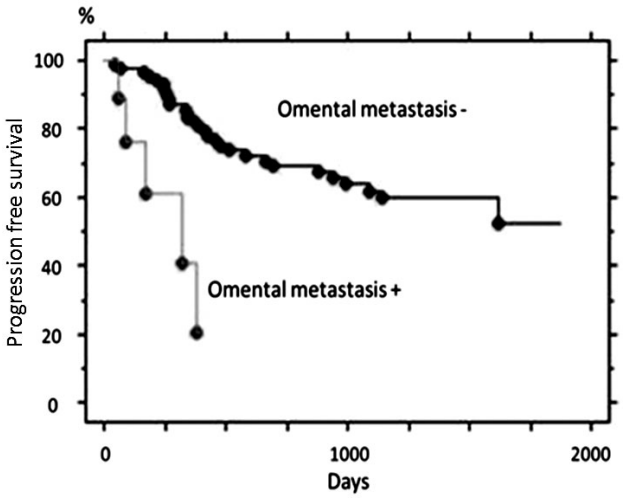


Figure 1. — Kaplan–Meier curves of progression-free survival in cases with omental metastasis and without metastasis. Patients with omental metastasis revealed significantly poorer prognoses compared with that in patients with no metastasis ($p < 0.001$).

sion were higher. The specificity of the macroscopic peritoneal dissemination and adnexal metastasis were higher.

*Prognosis*

Figure 1 represents Kaplan–Meier curves for the progression-free survival of cases with and without omental metastasis. Except for one case with a short follow-up period (seven months), all cases with omental metastasis suffered relapse and revealed a significantly poorer prognosis ($p < 0.001$).

## Discussion

The significance of omentectomy remains controversial in endometrial cancer. According to the NCCN guidelines, omentectomy is considered essential in cases with increased CA125 levels and in non-endometrioid histological type of cancers (serous adenocarcinoma, clear cell adenocarcinoma, and carcinosarcoma). It has been reported that the incidence of complications did not increase because of omentectomy, although partial omentectomy under the transverse colon occupied approximately 12–20 minutes of surgical time [11].

Omental metastasis was detected in 9% endometrial cancer cases in this study, which does not comply with results of past studies (3%–8%) [10, 12, 13]. The cases with omental metastasis were classified as Stage IVB according to the FIGO 2008 staging. In cases classified as Stage IVB, prognosis is assumed to be poor; one study reported a median overall survival of 24 months for such cases [14]. Although the therapeutic significance of omentectomy is thus unclear based on previous studies. With regards to the poor prognosis, confirmation of the presence of omental metastasis in clinical Stage I is very important.

There was a prospective analysis for the investigation of omental metastasis in clinical Stage I [13] and a retrospective study on the limited histological type of endometrioid adenocarcinoma [11]. These reports demonstrated that there remains the possibility that some omental metastasis could not be detected in those studies although omental metastasis existed.

Previous studies discussed predictive factors for omental metastasis. Chen *et al.* [13] reported that following pathological factors revealed significant correlation with omental metastasis: serous adenocarcinoma, adnexal metastasis, peritoneal dissemination around the Douglas' pouch, lymph node metastasis, and endometrioid adenocarcinoma G3. Dilek *et al.* [12] reported that adnexal metastasis, lymph node metastasis, and deeper myometrial invasion were correlated, and Fujiwara *et al.* [10] and Metindir *et al*. [11] reported that positive peritoneal cytology revealed significant correlation with omental metastasis. Other previous reports had discussed these predictive factors, but the significance of this correlation does require further research. In the present study, following pathological factors did not contradict findings of previous studies: non-endometrioid histological type, macroscopic peritoneal dissemination, and adnexal metastasis.

In the present study, sensitivity was higher in cases with a non-endometrioid histological type, specificity was higher in cases with macroscopic peritoneal dissemination and adnexal metastasis, and all nine cases with omental metastasis involved one of the three pathological factors. If we consider these three factors in preoperative and intraoperative stages, omentectomy should be performed in order not to miss omental metastasis.

In the present study, omental metastases were detected in about 1/3 cases with serous adenocarcinoma, and peritoneal dissemination was also often detected in cases with serous adenocarcinoma. Slomovitz *et al.* [15] reported that extrauterine spread was detected in 38% of 32 serous adenocarcinoma cases without myometrial invasion (endometrial intraepithelial carcinoma, EIC). On the basis of these findings, omentectomy should be performed in cases with presumed serous adenocarcinoma following preoperative endometrial biopsy.

In Case 1 from the present study, no peritoneal dissemination was suspected on preoperative CT, MRI, and intraoperative observation (Table 2). Moreover, no myometrial invasion, LVSI, adnexal metastasis, or lymph node metastasis was detected on postoperative pathological diagnosis, although microscopic omental metastasis was detected. In this case, the indication for omentectomy was based on the presence of non-endometrioid histological type—serous adenocarcinoma. If omentectomy had not been performed in this case, this patient would have been classified as Stage IA (i.e., early cancer). In our study, all cases had positive peritoneal cytology findings; however, no previous studies

have discussed the determination of surgical procedure based on rapid intraoperative peritoneal cytology. Further studies on the accuracy of rapid intraoperative peritoneal cytology and the relationship between cytology and determination of surgical procedure are needed.

## Conclusion

During the surgical therapy for endometrial cancer, omentectomy was shown to be beneficial in the exact surgical staging in cases with non-endometrioid histological type cancers, adnexal metastasis, and macroscopic peritoneal dissemination.

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