# The role of omentectomy in the surgical treatment of uterine serous carcinoma

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ARTICLE INFO

ABSTRACT

*Objective:* The aims of this study were to assess the role of omentectomy in the staging of uterine serous carcinoma (USC) and to evaluate its impact on patient outcomes.
*Study design:* Patients diagnosed with USC at the First Affiliated Hospital of Sun Yat-sen University of China were retrospectively reviewed. The clinicopathological characteristics and survival data of 187 patients were analyzed. Risk factors for omental metastasis were evaluated. Kaplan–Meier survival curves were used to compare survival status and the presence of omental metastasis.
*Results:* We found that 35 of 187 patients (18.7%) had omental metastases. Omental metastasis was significantly associated with adnexal involvement (40.0% vs 19.1%, P = 0.008, OR 2.828, 95% CI 1.286–6.218). Multivariate analysis showed that in addition to lymph node metastases and suboptimal surgery, omental metastasis in USC remained an independent predictor of decreased PFS and OS (PFS, HR 1.48, 95% CI 1.14–4.63, P = 0.024; OS, HR 1.39, 95% CI 1.04–3.60, P = 0.043).
*Conclusions:* The incidence of omental metastasis is not low in patients with USC. Visual assessment and omental biopsy may be insufficient for recognizing occult metastases. Omentectomy should be part of the staging surgery in USC patients because it provides additional information about survival. Prospective studies are needed to confirm these results.
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## Introduction

Endometrial carcinoma is the most common cancer of the female genital system worldwide, and its incidence has been rising due to the increasing incidence of obesity. A dualistic model of endometrial tumorigenesis and classification (type I and type II endometrial cancer) has been widely accepted [1]. Type I endometrial carcinoma is the most common type of endometrial cancer (80%–90%); it primarily includes endometrioid adenocarcinomas. In contrast, type II endometrial carcinoma (10%–20%) is often referred to as estrogen-independent and has a more complex etiology that is not yet fully understood.

Uterine serous carcinoma (USC) accounts for only 10% of all endometrial cancers but comprises most type II endometrial cancers [2]. It is a high-grade tumor with a substantially worse prognosis and frequent recurrence outside the uterus compared with endometrioid adenocarcinoma [3]. The tendency toward frequent distant metastasis exists even in tumors with apparently noninvasive intraepithelial lesions [4]. Thus, USC usually requires extensive surgery and adjuvant chemotherapy and/or radiotherapy. According to the NCCN guidelines, the principle of USC staging is total hysterectomy and bilateral salpingo-oophorectomy as well as lymph node assessment. Omental biopsy, but not omentectomy, is recommended [5]. However, considering that the omentum is frequently involved in metastasis to extrauterine sites, in addition to the ovaries and pelvic and para-aortic lymph nodes [6,7], whether omental biopsy is sensitive enough to evaluate the status of the omentum is still in doubt. Due to the comparatively low incidence of USC, randomized trials of therapies and outcomes of patients with these histologic subtypes are scarce. The occult findings of peritoneal metastases remain unclear.

Therefore, the purpose of this study was to evaluate the omental metastasis rate of USC and to determine the significance of routine omentectomy as part of comprehensive surgical staging in patients with USC.

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## Patients and methods

### Study eligibility

This is a single-center study with a retrospective cohort design. Approval to conduct this study was obtained from the Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University in China. We performed a thorough review of the medical records of patients with pathologically confirmed primary uterine serous tumors who underwent surgery at the First Affiliated Hospital of Sun Yat-sen University of China between January 1, 2009, and December 31, 2017.

Staging was performed according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) surgical staging criteria [8]. All surgical procedures were performed by gynecologic oncology surgeons at our institute. Surgical debulking is considered optimal when residual tumor nodules are less than 1 cm in maximum diameter or thickness [5,9]. The histological diagnoses were based on the World Health Organization criteria, and all microscopic slides were reviewed by 2 experienced gynecologic pathologists.

Clinical and pathological variables, including patient age, surgical procedure, and final pathology results (histological type and grade), were extracted from the patients' medical records.

The eligible criteria of this study were as follows: 1) As the Gynecologic Oncology Group Pathology Committee mandates that USC should comprise more than 50% of a mixed component tumor to be designated as USC for study protocol purposes [10], only patients with tumors showing a presence of serous components exceeding 50% were included in this study. 2) Only patients who underwent complete staging surgery, including hysterectomy, bilateral salpingo-oophorectomy, lymph node assessment and infracolic omentectomy for surgical treatment, were enrolled.

Patients with incomplete surgical or pathologic data were excluded from the study, as were patients with synchronous primary cancers. Patients whose data were lost to follow-up were also excluded.

Progression-free survival (PFS) was calculated as the number of months from the completion of primary treatment to the date of clinical recurrence. Overall survival (OS) was defined as the number of months from the completion of primary treatment to the date of death. Survival was calculated from the date of surgery until May 2018.

### Statistical analyses

Analyses of baseline characteristics and clinico-pathological variables were performed using Student's $t$-test and Fisher's exact test. Survival curves were constructed using the Kaplan-Meier method. The prognostic values of the clinicopathological parameters with respect to PFS and OS were evaluated via multivariate analysis (Cox proportional hazard regression test) and expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical analyses were performed using SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA). All tests were two-tailed, and results with $P < 0.05$ were regarded as statistically significant.

## Results

### Patient characteristics

In total, 187 patients with USC were identified in our study after careful evaluation of medical records. The baseline characteristics are shown in Table 1. The median age of the patients was 64 years (range, 32–84 years). All patients underwent hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic lymph

**Table 1**
Baseline patient characteristics.

| Patient demographics | N |
|---|---|
| **Age, years** | 64 (32–84) |
| **FIGO stage** | |
| IA | 40 (21.4%) |
| IB | 36(19.3%) |
| II | 12(6.4%) |
| IIIA | 19(10.2%) |
| IIIB | 4(2.1%) |
| IIIC | 32(17.1%) |
| IVA | 2(1.1%) |
| IVB | 42(22.5%) |
| **Lymphovascular Space Involvement** | |
| Present | 86(46.0%) |
| Absent | 101(54.0%) |
| **Depth of Myometrial Invasion** | |
| < 50% | 68(36.4%) |
| $\geq$ 50% | 119(63.6%) |
| **Peritoneal cytology** | |
| Positive | 46(24.6%) |
| Negative | 141(75.4%) |
| **Lymphadenectomy** | |
| Pelvic | 187 (100%) |
| Pelvic + para-aortic | 117(62.6%) |
| **Chemotherapy** | 155 (82.9%) |
| **Radiotherapy** | 114 (61.0%) |

Descriptive statistics were reported as median (range) or number (percentage).

node dissection, and 117 (62.6%) patients underwent para-aortic lymph node dissection. A total of 87 patients underwent staging surgery. One hundred patients underwent debulking surgery; 92 of these surgeries were optimal.

After comprehensive surgical staging and pathological evaluation, the distribution of the patients according to the International Federation of Gynecology and Obstetrics stages was as follows: 76 patients, stage I (40.6%); 12 patients, stage II (6.4%); 55 patients, stage III (29.4%); and 44 patients, stage IV (23.6%). A total of 155 patients received adjuvant chemotherapy for 3–8 cycles, which usually entailed combination therapy with carboplatin and paclitaxel. A total of 114 patients received adjuvant radiation.

### Prevalence of omental metastases

Overall, 35 out of 187 patients (18.7%) had omental metastases after surgical staging; 17 of these patients demonstrated occult disease, and 18 exhibited gross metastases. Among the patients with omental disease, 16 had uterine serosa and adnexa metastases, 7 had pelvic lymph node metastases, 2 with had peritoneum metastases, 5 had para-aortic lymph node metastases, 2 had appendix metastases and 4 had liver metastases. Peritoneal cytology was malignant in 12 of the patients (34.3%) who had omental metastases.

In total, 31 patients from the cohort (16.6%) were upstaged to stage IVB based on routine omentectomy. In all, 5, 6, 2, 9 and 9 patients were upstaged from intraoperative stage IA, IB, II, IIIA, and IIIC, respectively, to a final stage of IVB after omentectomy.

### Risk factors for omental metastasis

The characteristics of patients with USC based on omental metastases were examined (Table 2). Omental metastases were significantly associated with adnexal involvement, and there were more patients with adnexal involvement in the omental metastasis-positive group compared to the omental metastasis-negative group (40.0% vs 19.1%, P = 0.008, OR 2.828, 95% CI 1.286–6.218). There were also more patients with omental metastases in the deeper myometrial invasion group, but this difference was not

**Table 2**
Clinico-pathologic characteristics of women with uterine serous carcinoma based on omental status.

| Characteristics | Omental metastases (+) | Omental metastases (−) | P value OR (95%CI) |
|---|---|---|---|
| **Age** | | | 0.454 0.730(0.343–1.555) |
| < 60 | 13(37.1%) | 68(45.7%) | |
| ≥ 60 | 22(62.9%) | 84(54.3%) | |
| **Tumor diameter** | | | 0.288 0.648(0.290–1.447) |
| < 2 cm | 10(28.6%) | 58(38.2%) | |
| ≥ 2 cm | 25(71.4%) | 94 (61.8%) | |
| **Peritoneal cytology** | | | 0.084 1.811 (0.817–4.011) |
| Positive | 12(34.3%) | 34(22.4%) | |
| Negative | 23(65.7%) | 118(77.6%) | |
| **Depth of myometrial invasion** | | | 0.069 2.030(0.950–4.339) |
| < 50% | 15(42.9%) | 41(29.9%) | |
| ≥ 50% | 20(57.1%) | 111(70.1%) | |
| **Lymphovascular space involvement** | | | 0.275 1.507(0.720–3.152) |
| Absent | 19(54.3%) | 67(44.1%) | |
| Present | 16(45.7%) | 85(53.9%) | |
| **Adnexal involvement** | | | **0.008** 2.828(1.286–6.218) |
| Present | 14(40.0%) | 29(19.1%) | |
| Absent | 21(60.0%) | 123(80.9%) | |

statistically significant (57.1% vs 42.9%, P = 0.069, OR 2.030, 95% CI 0.950–4.339). No significant association was found between the presence of omental metastasis and age (P = 0.454), tumor diameter (P = 0.288), peritoneal cytology (P = 0.084), or LVSI (P = 0.275).

*Omental metastasis and survival analysis*

The median follow-up time was 46 months (range, 3–109 months). There were 144 cases of recurrence or disease progression and 103 deaths reported in the study cohort. The median PFS and OS were 16 and 46 months, respectively.

Upon univariable analysis, omental metastasis was significantly associated with PFS and OS (Fig. 1, both P < 0.001). The PFS and OS of those who had omental metastases were 9 and 22 months, respectively, while the PFS and OS for those without omental metastases were 18 and 48 months, respectively. Multivariate analysis showed that after other clinicopathological characteristics were controlled for (Table 3), omental metastases in USC remained an independent predictor of decreased PFS and OS (PFS, HR 1.48, 95% CI 1.14–4,63, P = 0.024; OS, HR 1.39, 95% CI 1.04–3.60, P = 0.043). Lymph node metastases and suboptimal

surgery also remained independent prognostic factors for decreased PFS and OS.

**Discussion**

In this study, we found that the rate of omental involvement was 18.7% in women with USC, half of whom demonstrated occult omental diseases. Additionally, omental metastases were significantly related to PFS and OS. Therefore, based on our findings, we strongly recommend omentectomy, rather than merely omental biopsy, as a routine component of surgical staging for USC.

Although it arises in the endometrial cavity, USC shares more similarities with serous ovarian cancer than it does with uterine endometrioid carcinoma. Its biological behavior is aggressive. Comprehensive staging surgery is a widely accepted approach for these histological types of cancer. The reasons behind this strategy are the propensities of USC to shed cells and metastasize widely to extrauterine sites. However, it is not clear whether omentectomy should be part of staging surgery. The NCCN guidelines recommended omental biopsy for USC, while the first joint ESMO-ESGO-ESTRO consensus conference considered that omentectomy should be performed in serous subtypes [11].
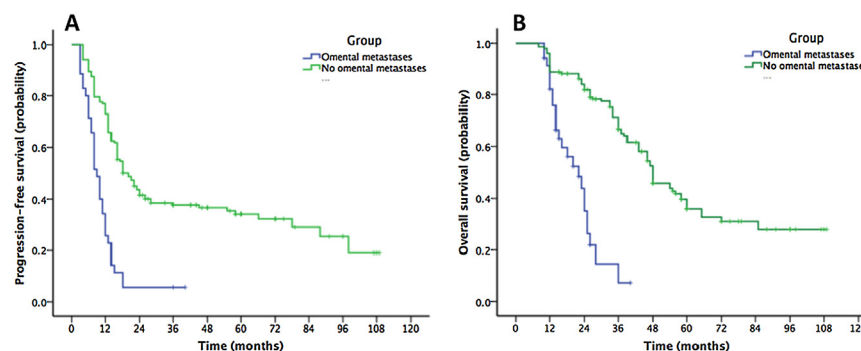


**Fig. 1.** Kaplan–Meier survival curves of progression-free survival and overall survival in patients with and without omental metastases (A: progression-free survival curve; B: overall survival curve).

**Table 3**
Multivariate analyses of all patients for PFS and OS.

| Characteristics | Progression-free survival | | | Overall survival | | |
|---|---|---|---|---|---|---|
| | HR | 95 % CI | P | HR | 95 % CI | P |
| **Age** | | | 0.36 | | | 0.26 |
| ≤ 60 | 1 | – | | 1 | – | |
| > 60 | 1.46 | 0.75-2.67 | | 1.58 | 0.88-3.62 | |
| **Tumor diameter** | | | 0.24 | | | 0.37 |
| < 2 cm | 1 | – | | 1 | – | |
| ≥ 2 cm | 1.23 | 0.86-1.89 | | 1.53 | 0.75-3.17 | |
| **Peritoneal cytology** | | | 0.42 | | | 0.68 |
| Positive | 1 | – | | 1 | – | |
| Negative | 1.37 | 0.64-2.42 | | 1.06 | 0.59-1.84 | |
| **Depth of myometrial invasion** | | | 0.225 | | | 0.183 |
| < 50% | 0.72 | 0.58-1.44 | | 0.79 | 0.66-1.21 | |
| ≥ 50% | 1 | – | | 1 | – | |
| **Lymph node metastases** | | | **0.003** | | | **0.016** |
| Absent | 1 | – | | 1 | – | |
| Present | 2.68 | 1.28-6.49 | | 3.20 | 1.35-12.8 | |
| **Lymphovascular space involvement** | | | 0.18 | | | 0.258 |
| Absent | 1 | – | | 1 | – | |
| Present | 1.79 | 0.84-2.55 | | 1.62 | 0.74-2.13 | |
| **Omental metastases** | | | **0.024** | | | **0.043** |
| Absent | 1 | – | | 1 | – | |
| Present | 1.48 | 1.14-4.63 | | 1.39 | 1.04-3.60 | |
| **Cytoreductive surgery** | | | <**0.001** | | | <**0.001** |
| Optimal | 1 | | | 1 | | |
| Suboptimal | 2.96 | 1.78-5.98 | | 3.58 | 2.16-6.33 | |

The prevalence of omental metastasis in USC ranged from 10 to 17.4% [12–14]. Even in women with noninvasive serous carcinoma limited to the endometrium, the occurrence of omental metastases was as high as 5.1–9.8% (58/591) in clinical stage I nonendometrioid type endometrial cancer [15,16]. Moreover, the rate of microscopic omental metastases cannot be neglected. Young et al. found that in apparent early EOC, approximately 30% of cases were truly at an advanced stage due to microscopic spread to the abdomen, including the omentum [17]. One meta-analysis reported that the prevalence of omental metastases in clinical stage I cancer, including nonendometrioid type cancer, was 9.8% (58/591), which was significantly higher than the prevalence in endometrioid type cancer [16]. A similar result was found in our study, as the occurrence of occult omental disease was 9.1%. Kaban et al. reported that 44.1% of omental diseases exhibited occult metastases in nonendometrioid-type endometrial cancers, and the sensitivity of a surgeon's visual assessment of the omentum (positive or negative) was 0.55 [14]. This suggests that visual assessment of the omentum is insufficient for recognizing these often occult metastases.

The question of whether the omentum plays a beneficial or harmful role in cancer has been debated for a long time. For over a century, the omentum has been considered a defender of the peritoneal cavity. However, although the omentum may be able to trap cancer cells and destroy them [18], this ability was not enough to prevent peritoneal tumor outgrowth in a rat model [19]. We prefer omentectomy to omental biopsy in USC cases for the following reasons. First, optimal debulking is linked to significant improvement of survival in ovarian cancer. Work by Nieman et al. suggested that ovarian cancer cells use the adipose found in the omentum as fuel to increase growth and spread, as evidenced by their increased expression of FABP4 Va protein, which allows for the uptake and metabolism of fatty acids [20]. USC is an aggressive histologic subtype of endometrial cancer with a metastatic pattern similar to that of ovarian cancer, and it accounts for a disproportionate number of recurrences and deaths [21,22]. Maximal tumor debulking is recommended, which is similar to the recommendations for ovarian cancer [23]. Patients with omental metastases are categorized as having stage IV USC and

are expected to have a very poor prognosis. Our study showed that omental metastases were a risk factor for decreased PFS and OS. Ross et al. revealed that omental disease had a significant impact on survival (median OS 11.4 vs 128.7 months for those who did and did not have omental disease, respectively; P < 0.001) [24]. Second, adjuvant chemotherapy and targeted therapy might help improve the survival of patients with advanced endometrial cancer [25]. The occurrence of occult omental disease was not negligible (9.1% in our study); omentectomy will prevent residual effects of occult omental metastases and will provide more information about the extent of disease, which will help physicians to choose an appropriate adjuvant therapy [26,27]. Third, it should be noted that the omentum is a common site of recurrence. Rita Luz reported that the most frequent sites of recurrence or progression in USC were the peritoneum (31%), followed by the omentum (27%), pelvis (18%), lungs (18%), and liver (14%) [13]. Thus, omentectomy may reduce recurrence. Moreover, omentectomy is not a complicated procedure, and it seldom results in severe postoperative complications [24,28,29]. However, based on the existing data, it should be noted that the survival benefit of adding omentectomy to the treatment for USC when the omentum is normal in appearance is still uncertain [30]. More randomized control trials are needed.

Although the outcome of USC with omental metastases is poor, the prediction of omental involvement based on pathological features is unreliable, and several studies have found that the disease spread beyond the uterus, even in patients with non-myoinvasive USC [31–33]. In our series, 11 patients were upstaged from stage I to stage IV after omentectomy. Our multivariate analysis showed that adnexal invasion was a risk factor for omental involvement, which is consistent with the results obtained in Kaban's study [14]. Thus, adnexal involvement might predict the need for omentectomy. The relevant risk factors should be further explored prospectively.

The strengths of this study include the relatively large sample size for a rare gynecologic malignancy. Additionally, this is the first such study of a Chinese population. There are several limitations of this study. First, our study is limited by the retrospective data collection, the long study period, and possible referral bias. Second, this study is

based on the operative records of surgeons who subjectively evaluated peritoneal tissue involvement. Third, various adjuvant treatment modalities might have affected the validity of the outcome. However, given the low occurrence rate of USC, our study contributes to the limited body of knowledge on this topic. Multicenter prospective studies are needed to resolve this issue.

## Conclusion

In conclusion, omental metastasis is not uncommon in patients with USC. Visual assessment and omental biopsy may be insufficient for recognizing occult metastases. Our study supports the inclusion of omentectomy in staging surgery for USC patients. Prospective studies are needed to confirm these results.

## Role of the funding source

This study was funded by the National Natural Science Foundation of China81602261. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## Declaration of Competing Interest

All of the authors declare no conflict of interest.

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