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Risk factors for omental metastasis and the effect of omentectomy on survival in type 2 endometrial cancer patients

Varol Gülseren^{a,*}, İlker Çakır^b, Esra Canan Kelten^c, Aykut Özcan^b, Muzaffer Sancı^b, Ertuğrul Şen^a, Zübeyde Emiralioglu Çakır^b, İsa Aykut Özdemir^d, Kemal Güngördük^e

^a Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, School of Medicine, Erciyes University, Kayseri, Turkey

^b Department of Obstetrics and Gynecology, Tepecik Education and Research Hospital, İzmir, Turkey

^c Department of Medical Pathology, Tepecik Education and Research Hospital, İzmir, Turkey

^d Department of Obstetrics and Gynecology, Medipol University, Division of gynecologic oncology, İstanbul, Turkey

^e Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Muğla Sıtkı Koçman University, Faculty of Medicine, Muğla, Turkey

A B S T R A C T

To investigate the risk factors for occult omental metastasis and the effect of omentectomy on the survival of type 2 endometrial cancer (EC) patients. This study enrolled patients who were diagnosed with high-risk (grade 3, serous, clear cell, undifferentiated, carcinosarcoma, or mixed type) EC between 2000 and 2021 and underwent surgery in our center. Data from 482 patients were analyzed retrospectively. Omentectomy was performed in 405 (84.0%) patients. Omental metastases were detected in 61 (12.7%) patients. Eighteen (29.5%) of these metastases were occult. Adnexal involvement, malignant cytology, and peritoneal spread were independent risk factors for omental metastasis. The 5-year overall survival (OS) rate was 59.5% in patients who underwent omentectomy and 64.7% in those who did not ($P = 0.558$). In patients with and without omental metastases, the overall 5-year OS rates were 34.9% and 63.5%, respectively ($P < 0.001$). The 5-year OS rates of patients with a normal omentum, gross tumors, and occult metastases were 63.5%, 26.9%, and 52.5%, respectively ($P < 0.001$). Omental metastases is not uncommon in type II endometrial

* Correspondence to: Varol Gülseren, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, School of Medicine, Erciyes University, Kayseri 38039, Turkey.

E-mail address: drvarolgulseren@gmail.com (V. Gülseren).

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cancer; approximately one third of patients have occult metastases. Factors - positive cytology, adnexal involvement, and peritoneal involvement are associated with higher probability of omental metastases.

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Introduction

Endometrial cancer (EC) is the most common cancer of the female genital tract.¹ ECs with a high risk for recurrence are type 2 (clear cell, serous, undifferentiated, carcinosarcoma, and grade 3) tumors.² In particular, serous cancers spread from the peritoneal surfaces, similar to ovarian cancer.³ Methods to evaluate peritoneal spread include omentectomy, peritoneal biopsies, and peritoneal cytology sampling. Even with thorough exploration, cases of microscopic omental spread are not uncommon.⁴⁻⁶ The poor prognosis of serous-type cancer is due to its propensity to metastasize without known intrauterine risk factors for metastasis, such as deep myometrial invasion and lymphovascular space invasion (LVSI). Serous-type cancer has a unique pattern of spread to peritoneal tissues and a high rate of recurrence.⁷ The European Society of Gynecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO), and European Society of Pathology (ESP) recommend omentectomy for serous, carcinosarcoma, and undifferentiated cancers.⁸ It has been reported that omentectomy is not mandatory in a clinically normal-appearing omentum with clear cell and endometrioid cancers.⁸ However, omental metastases in clear cell tumors are not very rare (10%).²

The omentum is a visceral adipose tissue-derived from mesothelial cells. Omentectomy, particularly when performed laparoscopically, prolongs the operation time and may be associated with an increased risk of bleeding or postoperative ileus, as well as increased costs.⁶ Adipose hypertrophy in the omental region is associated with dyslipidemia and insulin resistance. Omentectomy can affect the metabolism of adipokines, which play a role in metabolic diseases such as type 2 diabetes and obesity.⁹ Considering these functions of the omentum, which of these patients should receive adjuvant chemotherapy must be determined, as most patients should undergo omentectomy. This study aimed to identify the risk factors for occult omental metastasis and the effect of omentectomy on the survival of type 2 EC patients.

Materials and methods

Patient characteristics

This study enrolled patients who were diagnosed with high-risk (grade 3, serous, clear cell, undifferentiated, carcinosarcoma, mixed type) EC between 2000 and 2021 and underwent surgery in our center. Patients with a low-grade endometrioid tumor who did not undergo surgery or attend regular follow-ups were excluded from the study. Data from 482 patients were analyzed retrospectively. This study was approved by the local ethics committee (August 15, 2022, Decision No: August 16, 2022). All procedures were performed following the ethical standards of the institutional and/or national research committee, and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Operations performed during surgery, comorbid diseases, age, cancer antigen 125 (CA125) values, adjuvant treatment types, recurrence time, and localization and survival results were extracted from the patient files and analyzed. All histological slides were evaluated by gynecolo-

pathologists. The depth of myometrial invasion, cervical involvement, adnexal involvement, LVSI, peritoneal cytology results, and pelvic lymph node (LN), para-aortic LN, and omental metastasis status were taken from the pathology notes. The size of the largest tumor in the omentum was noted. Eight to twelve histopathological sections were cut from the normal-appearing omentum and examined. The presence of visible tumors in the omentum was determined from the surgical notes. The stages were determined according to the International Federation of Obstetrics and Gynecology (FIGO) 2023 EC staging system by evaluating the pathology results and surgery notes.¹⁰

Surgical procedure

All surgical procedures were performed by experienced gynecological oncology surgeons. The abdomen was entered via a midline incision. The duration of the surgery was defined as the time between making the first skin incision to placing the last suture in the skin. The mesentery and serosa of the small intestine, the mesentery and serosa of the colon, the peritoneum of Douglas, and the peritoneum above the bladder, omentum, paracolic area, liver serosa, sub-diaphragmatic peritoneum, and stomach were examined during exploration. Hysterectomy and bilateral oophorectomy were performed in all patients. Pelvic and para-aortic LN dissection and omentectomy were added to the procedure. The caudal border in the pelvic LN dissection process is the level of the deep circumflex iliac vein, and the cranial border is the level of the aortic bifurcation. Sites dissected as pelvic LNs were located above the external iliac vessels, in the obturator fossa, in the proximal parts of the internal iliac vessels, and above the common iliac vessels. The para-aortic LNs are located between the aortic bifurcation caudally and the level of the left renal vein cranially. The LNs located on the aorta, interaortacaval, and inferior vena cava were dissected.

Adjuvant treatment

Carboplatin/paclitaxel treatment was started 4 to 8 weeks after surgery in all patients for whom systemic treatment was recommended. Six courses of treatment were planned. The systemic treatment protocol was 5 to 6 AUC intravenous carboplatin on day 1 and 80 mg/m² intravenous paclitaxel on days 1, 8, and 15. This protocol could not be applied to 5 patients due to allergies. Cisplatin/doxorubicin was administered to 2 patients. Three patients with carcinosarcoma were treated with cisplatin/ifosfamide. External beam radiotherapy was delivered by targeting the lower common iliacs, external iliacs, internal iliacs, obturators, parametria, upper vagina/para-vaginal tissue, and presacral LNs (in patients with cervical involvement). Radiotherapy was administered to the entire common iliac chain and para-aortic LN region (1-2 cm above the renal vessel) in patients with paraaortic LN involvement.

Follow-up

The patients were followed up every 3 to 4 months for the first 2 years, every 6 months for the next 3 years, and once a year after 5 years. The vagina and cuff area of the controls were evaluated with a speculum. Pelvic region imaging was performed with transvaginal ultrasonography. Abdominal observations were made by whole abdominal ultrasonography. Computed tomography or magnetic resonance imaging of the entire abdomen was performed once a year. Interim evaluations and imaging were performed in cases with complaints or positive findings.

Statistical analysis

Mean \pm standard deviation values were calculated for numerical data and were compared with Student's *t*-test. Categorical data are expressed as numbers and percentages and were an-

alyzed with the chi-square test. Logistic regression analysis was used to identify risk factors for omental metastasis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the results. Survival analysis was performed with the Kaplan-Meier method and the log-rank test was used to compare the results. All statistical analyses were performed using SPSS software (ver. 20.0; IBM Corp., Armonk, NY). *P*-values < 0.05 were considered significant.

Results

General information

This study enrolled 482 patients with high-grade EC, and the demographic characteristics and pathological data of the patients are provided in Table 1. The most common histological type was grade 3 endometrioid tumor. The mean age of the patients was 62.1 ± 9.4 years. Pelvic LNs were dissected in 454 (94.2%) patients and para-aortic LNs were dissected in 399 (82.8%) pa-

Table 1
Demographic characteristics and pathology results of the study group.

	Characteristics (n: 482)
Age (years), mean \pm StD	62.1 \pm 9.4
Hypertension, n (%)	240 (49.8)
Diabetes mellitus, n (%)	134 (27.8)
CA125 (U/ml), mean \pm StD	66 \pm 227
High level CA125 (>35), n (%)	133 (27.6)
Histological type, n (%)	
- Serous	85 (17.6)
- Clear cell	32 (6.6)
- Carcinosarcoma	89 (18.5)
- Undifferentiated	9 (1.9)
- High grade endometrioid	152 (31.5)
- Mix	115 (23.9)
Hysterectomy type, n (%)	
- Type 1	421 (87.3)
- Type 2	61 (12.7)
Pelvic lymph node metastasis, n (%)	115 (23.9)
Paraaortic lymph node metastasis, n (%)	90 (18.7)
Omentectomy, n (%)	405 (84.0)
Omental metastasis, n (%)	61 (12.7)
- Gross	43 (70.5)
- Occult	18 (29.5)
Deep myometrial invasion, n (%)	285 (59.1)
Cervical involvement, n (%)	172 (35.7)
Adnexal involvement, n (%)	69 (14.3)
lymphovascular space invasion, n (%)	340 (70.5)
Tumor size (cm), mean \pm StD	4.9 \pm 2.3
Malignant cytology, n (%)	39 (8.1)
Peritoneal spread, n (%)	23 (4.8)
Stage, n (%)	
- IC	12 (2.5)
- IIC	266 (55.2)
- IIIA	22 (4.6)
- IIIB	7 (1.5)
- IIIC	108 (22.4)
- IVB	67 (13.9)
Adjuvant external beam radiotherapy, n (%)	410 (85.1)
Adjuvant chemotherapy, n (%)	345 (71.6)
Recurrence, n (%)	143 (29.7)
- Pelvic	15 (10.5)
- Distant or multiple	128 (89.5)

StD, standard deviation.

Table 2

Comparison of clinical features according to omental pathological results.

	Normal omentum (n= 344)	Gross metastasis (n= 43)	Occult metastasis (n= 18)	P
Age (years), mean \pm StD	62.3 \pm 9.8	61.2 \pm 6.5	68.3 \pm 6.4	0.023
CA125 (U/mL), StD	36 \pm 68	128 \pm 272	294 \pm 738	<0.001
High level CA125 (>35), n (%)	81 (24.8)	20 (50.0)	12 (66.7)	<0.001
Histological type, n (%)				0.303
- Serous	62 (18.0)	7 (16.3)	7 (38.9)	
- Clear cell	25 (7.3)	2 (4.7)	2 (11.1)	
- Carcinosarcoma	69 (20.1)	12 (27.9)	4 (22.2)	
- Undifferentiated	6 (1.7)	1 (2.3)	-	
- High grade endometrioid	96 (27.9)	10 (23.3)	-	
- Mix	86 (25.0)	11 (25.6)	5 (27.8)	
Pelvic LN metastasis, n (%)	77 (23.2)	14 (37.8)	8 (50.0)	0.012
Paraortic LN metastasis, n (%)	65 (21.1)	9 (25.7)	8 (53.2)	0.014
Deep myometrial invasion, n (%)	208 (60.5)	32 (74.4)	11 (61.1)	0.206
Cervical involvement, n (%)	124 (36.0)	23 (53.5)	10 (55.6)	0.028
Adnexal involvement, n (%)	31 (9.0)	21 (48.8)	11 (61.1)	<0.001
LVSI, n (%)	238 (69.2)	36 (83.7)	17 (94.4)	0.013
Tumor size (cm), mean \pm StD	4.8 \pm 2.0	6.5 \pm 3.6	3.8 \pm 2.6	<0.001
Malignant cytology, n (%)	17 (4.9)	14 (32.6)	7 (38.9)	<0.001
Peritoneal spread, n (%)	6 (1.7)	11 (25.6)	6 (33.3)	<0.001
Adjuvant EBRT, n (%)	318 (92.4)	17 (39.5)	3 (16.7)	<0.001
Adjuvant chemotherapy, n (%)	249 (72.4)	38 (88.4)	18 (100)	0.003
Recurrence, n (%)	99 (28.8)	26 (60.5)	7 (38.9)	<0.001
- Pelvic	13 (13.1)	1 (3.8)	1 (14.3)	
- Distant or multiple	86 (86.9)	25 (96.2)	6 (85.7)	0.401

EBRT, external beam radiotherapy; LVSI, lymphovascular space invasion; LN, lymph node; StD, standard deviation.

tients. Omentectomy was performed in 405 (84.0%) patients. Omental metastases were detected in 61 (12.7%) patients. Eighteen (29.5%) of these metastases were occult. Relapse occurred in 143 (29.7%) patients. The clinical features of the patients who underwent omentectomy and had a normal omentum are compared with those of gross tumor and occult metastasis patients in Table 2. The histological type of the tumor ($P = 0.303$) and presence of deep myometrial invasion ($P = 0.206$) did not differ significantly among these patient groups. CA125 levels were higher in patients with metastases ($P < 0.001$). The rates of adnexal involvement, LVSI, malignant cytology, and peritoneal spread were significantly higher in patients with a metastatic omentum.

Effect of omentectomy on metastasis

Recurrence was detected in 11 (14.3%) patients who did not undergo omentectomy and 132 patients (32.6%) who underwent omentectomy ($P = 0.001$). All of the recurrences in patients who did not undergo omentectomy were distant or multiple organ metastases. About 11% of metastases seen in patients who underwent omentectomy were pelvic and 88.6% were distant or multiple organ metastases. The location of the recurrence did not differ significantly between groups that did and did not undergo omentectomy ($P = 0.237$).

Effects of omentectomy on surgery

The duration of surgery was 102 ± 21 minutes in patients who underwent omentectomy and 98 ± 19 minutes in patients who did not ($P = 0.086$). Although the decrease in postoperative hemoglobin tended to be greater in patients who underwent omentectomy, no difference was found between the groups (2.1 ± 0.7 vs 1.9 ± 0.6 ; $P = 0.067$). The mean hospital stay was 6.4 ± 2.1 days in those who underwent omentectomy and 5.9 ± 2.2 days in those who did not

Table 3

Logistic regression analysis of factors that may predict omental metastasis.

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Elderly (≥ 60)	2.2	1.1-4.1	0.014	2.0	0.7-5.1	0.140
High CA125 (> 35)	3.7	2.0-6.6	<0.001	2.0	0.9-4.7	0.085
LN metastasis	2.3	1.2-4.2	0.005	0.5	0.2-1.2	0.123
Deep myometrial invasion	1.7	1.1-2.6	0.013	1.3	0.6-2.5	0.411
Cervical involvement	2.0	1.2-3.6	0.009	1.3	0.6-3.1	0.432
Adnexal involvement	11.1	5.9-20.7	<0.001	5.6	2.4-13.0	<0.001
LVSI	2.9	1.3-6.4	0.006	2.2	0.6-7.5	0.190
Malignant cytology	1.9	1.1-3.5	0.019	3.3	1.4-9.7	0.008
Peritoneal spread	13.5	6.7-27.2	<0.001	11.1	4.6-26.6	<0.001

CI, confidence interval; LN, lymph node; LVSI, lymphovascular space invasion; OR, odds ratio.

($P = 0.051$). The incidence of postoperative paralytic ileus symptoms was 16.3% in those who underwent omentectomy and 9.1% in those who did not ($P = 0.069$).

Predictive markers of omental metastasis

An evaluation of the risk factors to predict omental metastasis was performed by logistic regression analysis (Table 3). Adnexal involvement (OR = 5.6, 95% CI = 2.4-13.0), malignant cytology (OR = 3.3, 95% CI = 1.4-9.7), and peritoneal spread (OR = 11.1, 95% CI = 4.6-26.6) were independent risk factors for omental metastasis.

Survival analysis

According to the Kaplan-Meier survival analysis, the 5-year overall survival (OS) rate was 59.5% in patients who underwent omentectomy and 64.7% in those who did not ($P = 0.558$) (Fig 1A). The 5-year OS rates were 34.9% and 63.5%, respectively, in patients with and without omental metastases ($P < 0.001$) (Fig 1B). The 5-year survival rates of patients with normal omentectomy pathology results, gross tumors, and occult metastases were 63.5%, 26.9%, and 52.5%, respectively ($P < 0.001$) (Fig 1C). Significant differences were observed between normal and gross tumors ($P < 0.001$) and between normal and occult metastases ($P = 0.001$), but not between gross and occult tumors ($P = 0.128$).

Discussion

This study determined that omental metastases are not uncommon (12.7%) in type 2 EC patients. Adnexal involvement, malignant cytology, and peritoneal spread were independent risk factors for omental metastasis. A contribution of omentectomy to survival could not be demonstrated. However, the survival of patients with gross or occult metastases was shorter than that of those with a normal omentum. After LNs and the adnexa, the most common site of extrauterine involvement for EC is the omentum.¹¹ Although omentectomy may seem like a simple procedure, operative time can be prolonged, and bleeding and postoperative ileus can occur, particularly during minimally invasive surgery. Moreover, in addition to fat storage, the omentum has important biological functions, such as immune regulation, tissue regeneration, and endocrine functions.⁹ The changes that occur after omentectomy work in favor of anti-diabetic metabolism and against hyperlipidemia and metabolic syndrome.⁹ Therefore, the question arises as to whether all patients with type 2 tumors undergo omentectomy. This study was designed to investigate this question.

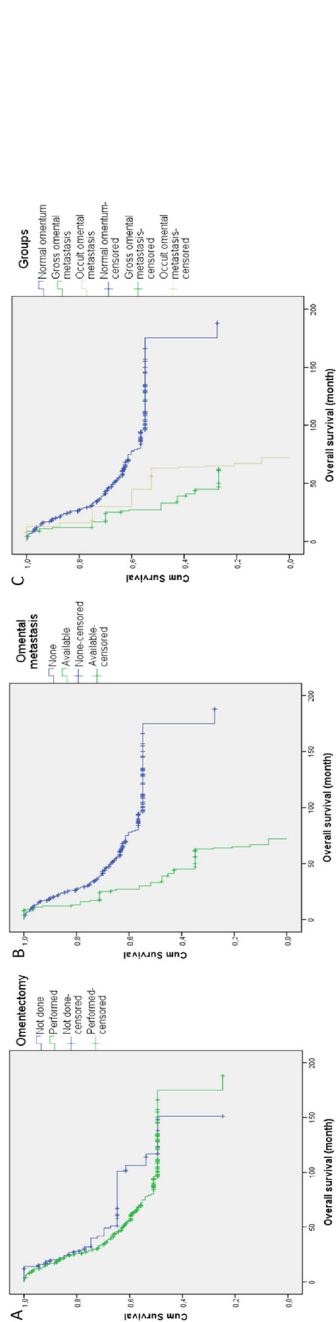


Fig. 1. According to the Kaplan-Meier method, the curve of performing omentectomy (1A), presence of omental metastases (1B), and type of metastasis (1C) versus overall survival. (Color version of figure is available online.)

Omental metastases were present in < 2% of patients with endometrioid-type low-grade tumors and in 14.8% of those with high-grade (III) tumors ($P=0.01$).¹² The rate of gross involvement of the omentum is 8% to 10% in type 2 tumors and 6% to 7% in occult metastasis, and the total metastatic rate is 9% to 18%.^{2,5,6,13} About one-quarter of omental metastases are occult.^{6,13} Although the ESGO recommends omentectomy for serous carcinosarcoma and undifferentiated tumors, the rates of metastasis in the omentum are similar between grade 3 endometrioid and clear cell cancers in the literature. In our study, omental metastases were detected in 9.4% (10/106) of patients with grade 3 tumors and 13.7% (4/29) of those with clear cell tumors, so these groups were included in the study. Omental metastases were seen in 12.7% of type 2 EC patients in our cohort, and approximately one-third of them had occult-type metastases.

The most common risk factors for omental involvement are adnexal involvement and malignant peritoneal cytology.^{2,6,11-13} In addition, other studies have demonstrated that LN metastasis, LVSI, and deep myometrial invasion are significantly more common in omental metastases.^{2,6} In our study, adnexal involvement, malignant cytology, and peritoneal involvement were independent risk factors for omental metastasis, which agrees with the literature.

Omentectomy did not have a significant effect on the survival of approximately 9000 patients with clinical stage I high-grade EC who underwent hysterectomy and LN dissection.¹⁴ Similar results were reported in patients with serous carcinoma.⁷ In our cohort, no significant difference in survival was detected between patients who did and did not undergo omentectomy. We think that the reason for this is that almost all patients with type 2 tumors are offered adjuvant systemic therapy. The rate of recurrence was significantly higher in patients who underwent omentectomy, probably because patients with gross tumors were included in the omentectomy group. It is not surprising that widespread intraabdominal involvement increases the probability of recurrence.

The omentectomy procedure can be performed as a total, infracolic, or wide biopsy. The mean size of occult omental metastasis is 0.3 cm.¹⁵ Many sections must be taken to locate the occult metastatic slide in a pathology specimen. However, as adjuvant chemotherapy is recommended for almost all patients with high-risk tumors, 3 to 5 samples were sufficient for appropriate staging, as ignoring the omental tumor does not affect the patient's treatment.¹⁵ Fujiwara et al. excised at least $10 \times 9 \times 5$ cm from the infracolic part of the omentum and performed a complete omentectomy if there was macroscopic suspicion of omental metastasis.¹⁶ This strategy seems to be the most acceptable.

Some limitations of this study should be discussed. First, this was a retrospective study, and some information in the related files may have been inaccessible. However, we believe that a sufficient number of patients with type 2 cancer of the endometrium benefited from this study to make a worthwhile contribution to the literature.

In conclusion, we determined that omental metastases is not uncommon in type II endometrial cancer; approximately one third of patients have occult metastases. The omentectomy procedure did not affect survival, and omentectomy should not be performed in some cases as chemotherapy is recommended for almost all patients (except stage IC); this is because it does not affect the decision for adjuvant treatment. Factors – positive cytology, adnexal involvement, and peritoneal involvement are associated with higher probability of omental metastases. Therefore, omentectomy may not be performed, or it may be performed in the form of a wide biopsy, to prevent complications, particularly during minimally invasive surgery.

Declaration of Competing Interest

The authors have declared none any conflict of interest.

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