

Prognostic significance of omental disease and the role of omentectomy in non-endometrioid endometrial cancer

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ABSTRACT

Objectives: Non-endometrioid endometrial cancers (non-EEC) have different management from endometrioid endometrial cancers. The purpose of this study was to investigate the prognostic significance of omental disease and the role of omentectomy in non-endometrioid endometrial cancer and discuss the current literature with the findings.

Material and methods: The study included two hundred-three patients with non-EEC who underwent surgical treatment and follow-up between January 1996 and December 2018 in a University Hospital Gynecologic Oncology Center. The patients were divided into three groups according to whether omentectomy was performed and the presence of omental metastasis. The patient's demographics, clinical characteristics such as stage, grade, histopathologic type, lymphovascular space invasion (LVSI), myometrial invasion, lymph node involvement, and survival outcomes were compared between the groups.

Results: The study included 203 patients. Twenty-five patients (12%) had omental metastases. LVSI was reported in 57.3%, 88.0%, and 43.2% of the non-omentectomy, no-omentectomy, and omental metastatic groups, respectively ($p = 0.001$). The 5-year disease-free survival (DFS) and overall survival (OS) rates according to the tumor grade, peritoneal cytology, and lymphadenectomy were also compared and were found to be statistically similar. The five-year OS rates were 70.6% for the group without omental metastases and 16.2% for the group with omental metastases, respectively ($p = 0.001$). In the group of omentectomy, the five-year DFS rates were 62.2% in cases without omental metastasis and 13.0% in cases with omental metastasis ($p = 0.001$). The five-year OS rates of 86.3% and DFS rates of 80.0% in the group without omentectomy.

Conclusions: In non-endometrioid tumors, the survival rate was better in the group that did not undergo omentectomy. Based on these results, we can say that omentectomy may not be necessary for non-endometrioid tumors whose omentum is found to be normal in intraoperative visual examination.

Keywords: endometrial cancer; non-endometrioid endometrial cancer; omentectomy; prognosis

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INTRODUCTION

Endometrial carcinoma is the most common cancer of the female genital system worldwide [1]. Endometrial tumors have traditionally been classified as endometrioid and non-endometrioid histologies and have different molecular and clinical features and outcomes. Non-endometrioid endometrial cancer (non-EEC) includes serous, clear cell, carcinosarcoma, undifferentiated, and mixed histology types

and is associated with a worse prognosis compared with endometrioid endometrial cancer (EEC) [2].

Patients with endometrial cancer are categorized into low, intermediate, high-intermediate, and high-risk profiles based on prognostic factors, which determine the choice of adjuvant treatment. Patients with non-EEC histology are considered as high risk. Management in this group of patients differs from patients with endometrioid carcinoma [3].

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Hysterectomy and bilateral salpingo-oophorectomy are the primary procedures for early-stage endometrial cancer. Additional staging is recommended for non-endometrioid high-grade tumors, such as serous and clear cell carcinomas.

Endometrial cancer metastasizes by direct invasion, hematogenous spread, lymphatic embolization, and peritoneal seeding. It is believed that peritoneal seeding and lymphatic spread contribute to omental dissemination [4]. Non-EEC has a higher incidence of extrauterine disease at presentation [5]. In the surgical treatment of endometrial cancer, omentectomy has been the topic of ongoing discussion for several years [2]. Significance and benefits of omentectomy in the surgical staging of EC are not well understood [6]. Due to the relatively low incidence of non-endometrioid tumors, outcomes for patients with these histologic subtypes are scarce. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology does not recommend omentectomy in the surgical staging criteria of EC; however, an omental biopsy is recommended [7, 8]. Some authors recommend omentectomy as part of staging instead of omental biopsy in serous carcinomas [9]. European Society of Gynecologic Oncology (ESGO) recommends an infracolic omentectomy in clinical stage I serous endometrial cancer, carcinosarcoma, and undifferentiated carcinoma, and stated that omentectomy can be omitted in stage I clear cell and endometrioid carcinomas [3]

The scarcity of literature regarding the importance of omentectomy in non-EEC encouraged us to conduct this study. Herein, we aimed to evaluate the rate of omental metastasis in non-endometrioid tumors, investigate its impact on survival, and determine the significance of routine omentectomy as a part of comprehensive surgical staging in these patients.

MATERIAL AND METHODS

The archival records and pathologic reports of patients with endometrial cancer who underwent surgery and follow-up in Çukurova University Gynecologic Oncology Center between January 1996 and December 2018, were reviewed, retrospectively. This study was performed in accordance with the ethical standards of the Helsinki Declaration. Ethical approval was obtained from the local ethics committee. Informed consent was obtained routinely. Demographic, pathologic, and follow-up data of the patients were collected. A total of 1114 endometrial cancer cases were screened. Patients with endometrioid and mucinous histologies were excluded. Fifteen patients were also excluded because of insufficient data. The remaining 203 patients were enrolled (Fig. 1). According to omental metastasis, patients were classified into two groups. Clinical and pathologic features, as well as oncologic outcomes,

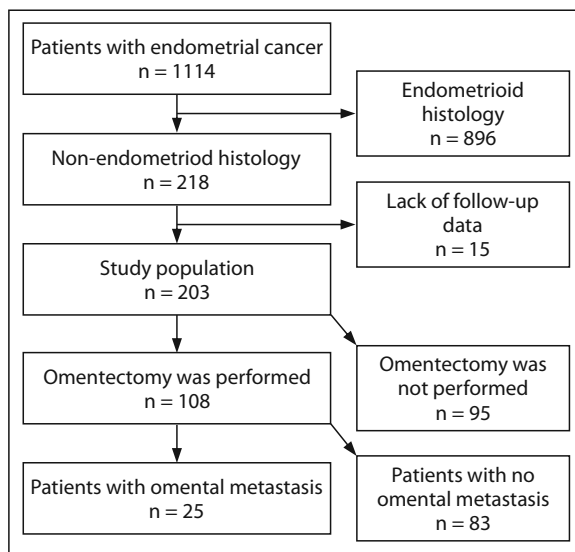


Figure 1. Flowchart of the study population

were compared between groups. The primary surgical methods were complete hysterectomy-bilateral salpingo-oophorectomy (by laparotomy or laparoscopy) with or without pelvic and para-aortic lymphadenectomy based on the results of intraoperative frozen sections. Omentectomy was performed as follows: first, an avascular plane anterior to the transverse mesocolon was discovered by cutting the posterior peritoneal fold covering the omentum where it attaches to the colon. Second, after cutting the posterior peritoneal fold of the omentum, the attachments at the level of the hepatic and splenic flexure were cut, and then the gastrocolic space was created. The omentum was separated from the transverse mesocolon. The stomach and the transverse colon were separated. The omentum was attached to the stomach, and the bursa omentalis was reached. After that, the omentum was separated from the hepatic flexure to the splenic flexure below the level of the greater curvature. The gastro-epiploic vessels were preserved.

The histologic diagnoses were based on the World Health Organization criteria and all microscopic slides were reviewed by experienced gynecologic pathologists.

The International Federation of Obstetrics and Gynecology (FIGO) 2009 endometrial cancer staging principles were used. The stages of cases registered before 2009 were reorganized appropriately. Patients were followed every three months for the first two years, then every six months for the next three years, and yearly thereafter. Disease-free survival (DFS) was defined as the time interval between the histopathologic diagnosis and recurrence. The time interval between histopathologic diagnosis and death was defined as overall survival (OS).

Statistical analysis

The SPSS software version 22.0 (IBM, Armonk, NY, USA) was used to analyze the data. Mean, standard deviation, median, and minimum-maximum values were used in the descriptive analysis. Chi-square or Fisher's exact tests were used to assess categorical data. The Kaplan-Meier technique was used to conduct the survival analysis, and the log-rank test was used to determine the differences in the survival curves. The Cox proportional hazard model was used to determine the significance of different factors. P values were considered significant at the 0.05 level.

RESULTS

During the study period, 1114 patients with endometrial cancer underwent surgery at our clinic. Among them, 203 patients were eligible for the study. Omental metastasis was diagnosed in 25 patients (12.3%). The study flowchart is shown in Figure 1.

The median age of the cohort was 57 (range 32–91) years. The average body mass index (BMI) was 31.2 ± 4.1 kg/m². The patients' clinical characteristics according to omental metastasis status are summarized in Table 1. Tumor type was serous in 5%, mixed in 10%, clear cell in 5%, and malignant mixed müllerian tumor in 5% of the omental metastasis group. Fifty-two percent (n = 107) of the patients were FIGO stage I. Age, menopausal status, BMI, surgical method (laparotomy or laparoscopy), comorbidities (e.g., diabetes mellitus, hypertension, cardiac or pulmonary disease), secondary cytoreductive surgery, postoperative complications, and adjuvant radiotherapy treatment rates did not vary between groups. LVSI was reported in 57.3%, 88%, and 43.2% of no-omental metastasis, omental metastasis and non-omentectomy groups, respectively (p < 0.001). The cervix was invaded in 45.8% of the omental metastasis group and 29.3% of the no-omental metastasis group (p = 0.031). No metastatic lymph nodes were detected in 75% (n = 155) of the patients. Pelvic lymph node metastases were detected in 8.5% (n = 19) of the patients, paraaortic metastasis in 6.3% (n = 13), and pelvic-paraaortic lymph node metastases were found in 6.8% (n = 15) of the patients. Lymph node metastasis rates were 10.7% (n = 21), 4.9% (n = 10), and 6.8% (n = 14), respectively (p = 0.01), according to omental metastasis (Tab. 2). Adjuvant treatment was administered to 84% (n = 140) of the patients. One patient refused to take chemotherapy in the omental metastasis group and adjuvant treatment was administered to 71% of patients in this group.

Survival analysis

The median follow-up time was 52.04 (range 6–209) months. OS and DFS analyses were performed with 200 patients because three patients were lost during follow-up.

The 5-year OS rates were 70.6% for the no-omental metastasis group and 16.2% for the omental metastasis group, respectively (p < 0.001). The 5-year DFS rates were 62.2% for the no-omental metastasis group and 13.0% for the omental metastasis group, respectively (p < 0.001). The five-year OS rates and DFS rates were 86.3% and 80.0% for patients who did not undergo omentectomy (Fig. 2).

Disease-free survival and OS rates were compared according to histology, grade, myometrial invasion, LVSI, FIGO stage, cytology, cervical invasion, omental metastasis, metastatic lymph node, and lymphadenectomy. The results are illustrated in Table 1.

The 5-year DFS rates according to the tumor grade, peritoneal cytology, and lymphadenectomy were also compared were not found to be a significant prognostic factor (p = 0.102, p = 0.061, and p = 0.409, respectively). On the other hand, according to the tumor histology, myometrial invasion, LVSI, FIGO stage, cervical invasion, omental metastasis, and metastatic lymph nodes, there were significant differences between the groups (p = 0.030, p < 0.001, p = 0.042, p < 0.001, p = 0.019, p < 0.001, and p = 0.006, respectively) (Tab. 3).

The 5-year OS rates according to LVSI and lymphadenectomy were not found to be a significant prognostic factor (p = 0.013 and p = 0.652, respectively). OS rates according to the tumor histology, grade, myometrial invasion, FIGO stage, cervical invasion, omental metastasis, and metastatic lymph nodes were significantly different between the groups (p = 0.007, p = 0.007, p < 0.001, p < 0.001, p = 0.010, p = 0.003, p = 0.001, and p < 0.001, respectively) (Tab. 3).

DISCUSSION

Non-endometrioid cancers have a worse prognosis than endometrioid cancers [10]. The surgical approach and treatment options also differ. It is known that the spread pattern of some types of non-endometrioid tumors is like that of ovarian cancer. In this line, our question was, whether it is clinically indicated to add omentectomy to the surgery of non-endometrioid EC. The majority of gynecologic oncologists perform omentectomy [3, 11–14]. It is also a matter of debate whether omentectomy should be performed in the presence of a macroscopic implant or in all cases. In the presence of macroscopic implants, omentectomy is already considered unconditional, but there are studies investigating the importance of microscopic metastases. In the study of Kaban et al. [15], the omental micrometastases rate was 44.1% of the metastases found in non-endometrioid tumors as occult metastases. They found the sensitivity of the surgeon's visual evaluation as 0.55. Kaban et al. [15] concluded that routine omental sampling was essential in non-endometrioid tumors, regardless of histopathologic subtypes.

Table 1. The factors determining 5-year disease-free survival (DFS) and overall survival (OS) in patients with non-endometrioid endometrial cancer — univariate analysis

Parameters	5-year DFS				5-year OS			
	N/n	[%]	Mean	p value	N/n	%	Mean	p value
Histology								
Serous	39/14	35.1	106	0.030	39/11	28.2	105	0.007
Clear cell	11/9	81.2	86		11/7	63.6	92	
Mixed	103/30	29.1	87		103/18	17.4	102	
MMMT	47/18	38.2	56		47/11	23.4	82	
Grade								
1	93/8	8.6	104	0.102	93/2	2.15	122	0.007
2	65/10	15.3	107		65/8	12.3	115	
3	42/10	23.8	81		42/6	14.2	102	
Myometrial invasion								
< 50	90/26	28.8	114	< 0.001	90/10	11.1	143	< 0.001
≥ 50	110/41	36.9	73		110/34	30.9	85	
LVSI								
No	91/24	26.3	116	0.042	91/12	13.1	138	0.013
Yes	109/45	41.2	68		109/34	31.1	86	
FIGO stage								
1	107/27	25.2	104	< 0.001	107/13	12.1	139	< 0.001
2	27/10	37.0	66		27/7	25.9	81	
3	61/28	45.9	58		61/24	39.3	77	
4	5/3	60	38		5/2	40	42	
Peritoneal cytology								
Negative	41/16	39.0	93	0.061	41/11	26.8	107	0.010
Positive	9/5	55.5	32		9/5	55.5	32	
Not taken	148/48	32.4	103		150/30	20	125	
Cervical invasion								
No	153/49	32.0	104	0.019	153/29	18.9	127	0.003
Yes	47/19	40.4	65		47/16	34.0	71	
Omental metastasis								
No	82/29	35.3	96	< 0.001	82/17	20.7	121	0.001
Yes	24/16	66.6	35		24/15	62.5	37	
No Oment-ectomy	94/22	23.4	110		94/12	12.7	125	
Metastatic lymph node								
No	156/45	28.8	106	0.006	155/26	16.7	108	< 0.001
Pelvic	17/10	5.8	73		17/8	47.0	98	
Paraaortic	12/6	50	62		12/8	66.6	26	
Pelvic and Paraaortic	15/5	33.3	48		15/5	33.3	56	
Lymph-adenectomy								
No	70/23	32.8	105	0.409	70/16	22.8	120	0.652
Yes	130/47	36.1	92		130/46	35.3	113	
Log-rank test								

N — total patients number; n — number of patients with omental metastasis; MMT — malignant mixed mullerian tumor; LVSI — lymphovascular space invasion; FIGO — International Federation of Obstetrics and Gynecology

Table 2. Patients' clinical characteristics

Parameters			With omentectomy				Without omentectomy		
			No omental metastasis		Omental metastasis		n	[%]	p value
			n	[%]	n	%			
Age	< 60	24	11	14	1	4.0	12	13	0.218
	> 60	179	72	86	24	96.0	83	87	
Menopausal Status	Pre-menopausal	17	5	6.0	1	4.0	11	10.6	0.389
	Post-menopausal	186	78	94.0	24	96.0	84	89.4	
BMI	< 30	71	25	30.3	6	23.4	40	42.2	0.271
	> 30	132	58	69.7	19	76.6	55	57.8	
Surgery Method	LT	148	76	91.6	24	96.0	48	50.5	NA
	LS	55	7	8.4	1	4.0	47	49.5	
Histology	Serous	39	24	29.9	5	20.0	10	10.5	0.021
	Clear cell	13	4	4.8	5	20.0	4	4.2	
	Mixed	105	31	37.3	10	40.0	64	66.3	
	MMMT	46	24	28.9	5	20.0	17	17.9	
Grade	1	93	35	32.1	2	8.1	56	52.3	NA
	2	65	26	30.3	8	32.4	31	38.3	
	3	45	22	39.2	15	59.5	8	9.3	
Myometrial invasion	< 50	90	41	49.4	6	24.1	66	69.1	NA
	≥ 50	113	42	50.6	19	76.9	29	30.9	
LVSI	No	93	36	43.3	3	12.0	54	56.8	< 0.001
	Yes	110	47	57.3	22	88.0	41	43.2	
FIGO Stage	1	107	44	53.0	0	–	62	65.2	NA
	2	28	14	16.8	0	–	12	12.6	
	3	61	22	26.5	0	–	20	21.0	
	4	7	3	3.6	25	100	1	1.0	
Recurrence	No	133	52	65.0	9	33.3	72	75.7	NA
	Yes	70	31	37.3	16	66.7	23	24.2	
Comorbidities	No	83	35	42.1	8	29.2	40	42.1	0.488
	Yes	120	48	57.8	17	70.8	55	57.9	
SCS	No	196	80	96.4	24	96.0	92	97.9	0.801
	Yes	7	3	3.6	1	4.0	3	2.1	
Post-operative Complications	No	179	68	85.0	22	88.0	89	93.6	0.131
	Infection	16	10	12.5	1	4.0	5	5.2	
	Urinary complications	5	5	0.0	0	0.0	0	0.0	
	Intestinal complications	3	0	0.0	2	8.0	1	1.1	
Cytology	Negative	43	23	27.5	5	16.7	15	15.7	NA
	Positive	10	2	1.3	6	25.0	2	2.1	
	Not taken	150	58	71.3	14	58.3	78	82.1	
Cervical invasion	No	153	58	70.7	14	54.2	81	85.3	0.031
	Yes	50	25	29.3	11	45.8	14	14.7	
Metastatic lymph node	No	155	61	74.4	14	58.3	80	84.1	0.010
	Pelvic	19	7	8.5	2	4.2	10	10.6	
	Paraaortic	13	4	4.9	6	25.0	3	3.2	
	Pelvic and Paraaortic	15	10	12.2	3	12.5	2	2.1	
Adjuvant treatment	No	59	13	15.7	1	4.0	45	49.5	NA
	Yes	140	70	84.3	24	96.0	46	50.5	
RT	No	122	46	56.1	18	72.0	58	63.0	0.195
	Yes	81	37	43.9	7	28	37	36.9	
CT	No	95	24	28.9	4	16.0	65	67.4	NA
	Yes	108	57	71	21	84	30	32.7	
Lymphadenectomy	No	71	5	6.0	11	41.7	55	57.9	NA
	Yes	132	78	94.0	14	58.3	40	42.1	

BMI— body mass index, LT—laparotomy; LS — laparoscopy; NA—not applicable; MMT— malignant mixed mullerian tumor; LVSI — lymphovascular space invasion; FIGO — International Federation of Obstetrics and Gynecology; SCS — secondary cytoreductive surgery; RT — radiotherapy; CT — chemotherapy

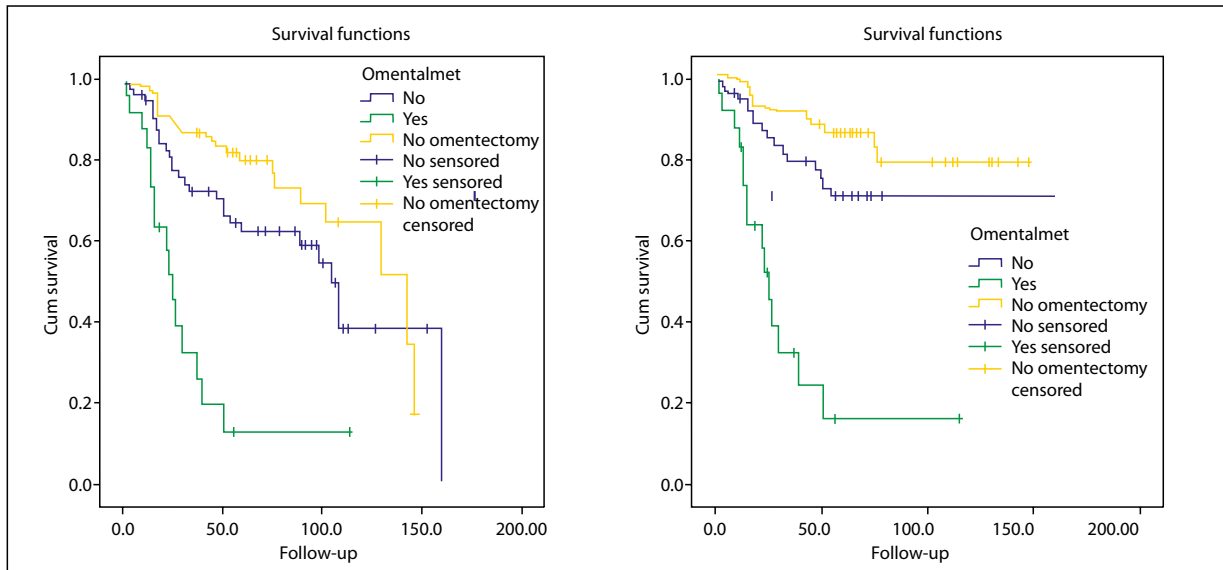


Figure 2. Survival curves with respect to the omental metastasis. Kaplan-Meier survival curves of disease-free survival and overall survival in patients with omental metastases, without omental metastases, and patients who did not undergo omentectomy (no omentectomy group); **A.** Disease-free survival curve; **B.** Overall survival curve

Table 3. Multivariate analysis of disease-free survival (DFS) and overall survival (OS)

Variable	DFS				OS			
	HR	(95% CI)		p value	HR	(95% CI)		p value
		Min	Max			Min	Max	
Histology	0.965	0.738	1.262	0.793	0.851	0.630	1.149	0.292
Cervical invasion	0.966	0.499	1.861	0.919	1.372	0.657	2.868	0.400
Omental metastasis	0.861	0.638	1.163	0.330	1.002	0.689	1.456	0.993
CT	0.997	0.780	1.274	0.981	1.105	0.795	1.536	0.551
MI	2.319	1.271	4.231	0.006	3.821	1.671	8.739	0.001
LN metastasis	0.733	0.331	1.625	0.445	0.971	0.387	2.177	0.845
FIGO stage 4	1.718	1.149	2.569	0.008	1.728	1.062	2.813	0.028

HR — hazard ratio; CI — confidence interval; CT — chemotherapy; MI — myometrial invasion; LN — lymph node; FIGO — International Federation of Obstetrics and Gynecology

There are different opinions about whether inspection during surgery is sufficient to detect omental metastases. Saygili et al. strongly recommended histopathologic examination, whereas Fujiwara et al. stated that this was not necessary and that inspection would be sufficient [12, 16]. However, there is no randomized controlled study on this subject and it has not been proven that total omentectomy contributes to survival [6]. Turan et al. found no difference in survival in relation to the presence of micrometastases and macrometastases [6]. Chen et al. [17], in their study evaluating serous carcinomas, reported that the rate of omental metastasis was 18.7%, and occult omental metastasis was 9.1%. Based on these findings, they recommended omentectomy in serous carcinoma. However, there is still some debate over

the survival advantage of omentectomy in uterine serous carcinomas, even in cases when the omentum seems normal. There is a need for a randomized control study.

In studies evaluating all histopathologic types in endometrial cancer, omental metastasis rates have been reported between 2.4% and 9% [6, 12, 15, 18]. These rates differ with tumor histopathology and stage. A study evaluating the mixed histologic type was reported omental metastasis rates as 9.1%, whereas it was 18.7% in serous carcinoma [19, 20]. In early-stage serous carcinomas, it is only 5.1–9.8% [21, 22]. In our study, the rate of omental metastases was 12.3% in total. According to histopathology, we detected 20% omental metastases in serous type, 5% in clear cell carcinoma, 10% in mixed tumors, and 5% in carcinosarcoma.

In another similar study, the rate of omental metastases was observed as 20.4%, 17.3%, 16.6%, and 10.0% in carcinosarcoma, serous, mixed subtypes, and clear cell types, respectively [15]. Considering these data, it can be said that omental metastasis may need to be handled separately in each type of non-endometrioid tumor. However, it may not always be possible to provide sufficient case numbers for such a study design.

Some authors stated that; the presence of adnexal metastases is a risk factor for omental metastases in non-endometrial tumors [15]. Lymph node metastasis, adnexal involvement, and peritoneal cytology positivity have been associated with omental metastasis different studies [18, 23]. In our study, the rate of lymph node metastasis was 25.6% in patients without omental metastasis, whereas this rate was 41.7% in patients with omental metastasis. The rates of peritoneal cytology positivity were 25% and 1.5% in patients with and without omental metastases, respectively. These rates support the relationship between omental metastasis and lymph node positivity, and cytology positivity.

Bayrak et al. [23] reported the rate of omental metastasis in their non-endometrioid group as 17.2%. Considering all endometrial cancer cases, the rate of metastasis was 5.3%. In the absence of macroscopic metastases, Bayrak et al. [23] found the rate of omental micrometastasis as 0.92%, and isolated paraaortic metastasis as 0.52%. Freij et al. [24] detected omental metastasis in only one patient in their study.

Chen et al. [17] stated that omental metastases are a risk factor that reduces progression free survival (PFS) and OS in uterine serous carcinoma. However, in a meta-analysis with many cases, Nasioudis et al. stated that performing omentectomy in high-grade patients did not contribute significantly to survival. They found that 3-year OS rates were 82.3% and 83%, respectively, in the group with and without omentectomy [25]. In patients with stage 1 high-grade endometrial carcinoma, there was no difference in overall survival between the omentectomy and non-omentectomy groups [25].

The retrospective design of our research is a limitation. In contrast, the key advantages of the research include its large number of patients. The examination of patients by the same professional team of gynecologic pathologists and gynecologic oncologists from an academic cancer center, and the long follow-up time.

CONCLUSIONS

In conclusion, performing omentectomy or not in non-endometrioid EC patients is still an issue of debate. However, it seems reasonable to omit omentectomy in non-endometrioid tumors with the normal appearance of the omentum during the intraoperative examination.

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

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