



Research Article

Investigation of Extra-Uterine Tumor Dissemination of Endometrial Cancers with Myometrial Invasion Less Than 50% According to Hystologic Subtypes

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Abstract

Objectives: To investigate the rates of extra-uterine metastases of non-endometrioid endometrial tumors limited to the half of the myometrium.

Methods: Patients operated for endometrial cancer between 2005-2015 in two gynecologic oncology centers were screened from clinical archives. The inclusion criteria were serous, clear cell, undifferentiated or carcinosarcoma histologies and less than half myometrial invasion. Each histological type was analyzed for adnexial metastasis, lymph node metastasis (pelvic/paraortic) and omental metastasis.

Results: A total of 116 patients with median age of 64 (34-72) were examined. Of the patients, 57 were serous (49.1%), 29 were clear cell (25.0%), 27 were carcinosarcoma (23.3%) and 3 (2.6%) were undifferentiated histologic type. Adnexial metastasis (over/tuba) was detected in 15 patients (12.9%), nodal metastasis in 10 patients (8.6%), and omental metastasis in 15 patients (12.9%). The rates of adnexial metastases were calculated as 14% for serous type, 10% for clear cell type and 11% for carcinosarcoma. Omental metastasis rates were 11% for serous type, 17% for clear cell type and 15% for carcinosarcoma. The rates of extra-peritoneal nodal metastases were calculated as 12% for serous type, 7% for clear cell type and 4% for carcinosarcoma.

Conclusion: According to this study, the rates of extra-uterin metastasis are high for serous, clear cell or carcinosarcoma types even in the early period. However, the lymph node metastasis in the carcinosarcoma seems to be lower. A comprehensive staging surgery should be planned for these patients, regardless of the depth of myometrial invasion.

Keywords: Endometrial cancer; myometrial invasion; extrauterin metastasis.

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Endometrial cancer (EC) is the seventh most common malignancy worldwide.^[1-3] In Turkey, EC is fourth cancer type after breast, thyroid and colorectal cancers.^[4]

Histologically, two subgroups are distinguished as endometrioid and non-endometrioid. Of these, ~ 10-20% are non-endometrioid types and have worse prognosis than

endometrioid type.^[5-8] These tumors originate from the endometrium, the innermost layer of the uterus, and the tumoral mass progresses locally to the myometrial tissue and serosal layer. According to the 2009 FIGO (The International Federation of Gynecology and Obstetrics) staging system, when the tumor progresses to the serosa, it is considered

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as stage-III.^[9] A tumor that does not exceed one half of the myometrium is accepted as an early period and is staged as IA according to FIGO. In endometrioid type tumors, it is considered that the rate of extra-uterine metastasis is very low in this period and comprehensive staging surgery is not necessary according to the recommendations of many guides including ESMO-ESGO-ESTRO.^[10]

Our aim of the study was to investigate the risk of extra-uterine metastasis in non-endometrioid endometrial carcinomas and to discuss the necessity of comprehensive staging surgery in the early period. For this, the presence of tumor in the adnex (over/tuba), omentum and lymph nodes (pelvic/paraortic) was investigated when the tumor was limited to the first half of the myometrium.

Methods

In this study, we have evaluated 116 cases who had undergone staging surgery for endometrium ca between 2005 and 2015 at Gynecological Oncology Departments of two Research and Education Hospitals. Patients with serous, clear cell, undifferentiated and carcinosarcoma histologic types whose myometrial invasion is less than one half were selected. Hysterectomy and bilateral salpingo oophorectomy plus lymphadenectomy and omentectomy were defined as staging operation. In this study, patients without lymphadenectomy and patients with very few lymph nodes removed (less than 6 lymph nodes) were excluded from the study regardless of the presence of paraortic lymphadenectomy. Pathologic data were obtained from post-operative pathology reports reported by gynecopathologists in both hospitals. The following findings of patients were recorded: Age, histological subtype, adnexal metastasis (fallopian tube/ovary), omental metastasis and lymph node metastases. Adnexal metastasis, omental metastasis and lymph node metastasis rates were calculated for each subtype.

Statistical Analysis

For statistical analysis, IBM SPSS Statistics Version 22 was used. Chi-square test and Fisher exact test were used for adnexal metastasis and omentum metastasis relation.

Ethical committee approval form was obtained from the Ethics Committee of Istanbul University (date: 9/3/2018 decision no: 05). All patients signed an informed consent that allowed our center to use their clinical data for scientific trials.

Results

One hundred sixteen patients with a median age of 64 (34-78) were included in the study. Of the patients, 57

were serous (49.1%), 29 were clear cell (25.0%) and 27 were carcinosarcoma (23.3%). In 3 patients (2.6%), undifferentiated adenocarcinoma was observed (Table 1). Eleven patients (12.8%) had adnexal (over/tuba) metastasis, 10 (8.6%) had lymph node metastasis, and 15 (12.8%) had omental metastases. Fifty-three percent of omentum metastases were macroscopic (n=8), 47% (n=7) were microscopic metastases. Omentum metastasis was most frequently seen in clear cell carcinoma (17%), followed by carcinosarcoma (15%) and serous adenocarcinoma (11%). The rate of nodal metastasis was highest in serous type (12%), followed by clear cell (7%) and carcinosarcoma (4%). Paraortic nodal metastasis was detected only in one patient. This patient had serous histology. Adnexal metastases were the most common in serous type (14%), followed by clear cell (10%) and carcinosarcoma (11%) (Fig. 1). Patients with adnexal metastasis had a significantly higher percentage of omentum metastases (47% and 8%, $p=0.001$) (Table 2). When we consider the relationship between omental micrometastasis and adnexal metastasis, we found that the rates of micrometastasis in omentum were higher in patients with adnexal metastasis, but the difference was not significant (5% and 13%, $p=0.223$) (Table 3).

Table 1. Outcomes of extra-uterine metastases in 116 patients with non-endometrioid endometrium cancer with a myometrial invasion rate of less than 50%

Feature	p
Age (year), median	64 (34-78)
Histological type, n %	
Serous	57 (49.1)
Clear-cell	29 (25.0)
Carcinosarcoma	27 (23.3)
Undifferentiated	3 (2.6)
Locations of extra-uterine metastasis, n %	
Adnexal metastasis	15 (12.9)
Omentalmetastasis	15 (12.9)
Macroscopic	8
Microscopic	7
Lymph node metastasis	10 (8.6)
Rates of omental metastases, %	
Serous	11%
Clear-cell	17%
Carcinosarcoma	15%
Rates of nodal metastases, %	
Serous	12%
Clear-cell	7%
Carcinosarcoma	4%
Rates of adnexal metastases, %	
Serous	14%
Clear-cell	10%
Carcinosarcoma	11%

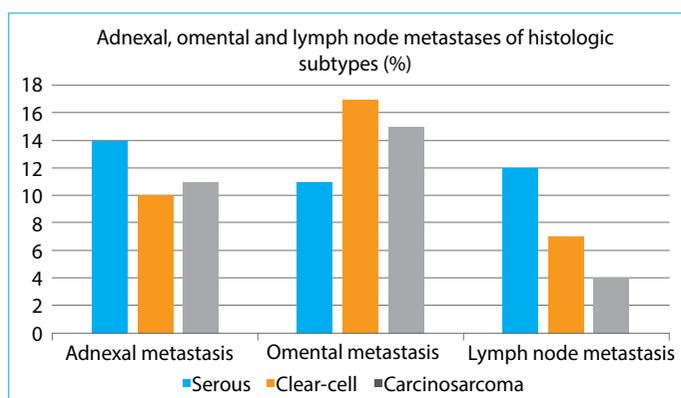


Figure 1. Adnexal, omental, and lymph node metastasis of histological tumor types.

Table 2. Risk of omentum metastasis in patients according to presence of adnexal metastasis

Omental metastasis	Adnexal metastasis		Total	p
	No	Yes		
No metastasis	93 (92%)	8 (53%)	101	0.001
Present metastasis	8 (8%)	7 (47%)	15	
Total	101	15	116	

Table 3. Assessment of microscopic omentum metastasis in the presence of adnexal metastasis

Micrometastasis at omentum	Adnexal metastasis			p
	No	Yes	Total	
No micrometastasis				0.223
Present micrometastasis	96 (95%)	13 (87%)	109	
Total	5 (5%)	2 (13%)	7	
Total	101	15	116	

Discussion

The aim of the study was to discuss whether a comprehensive staging surgery was necessary in early stage non-endometrioid endometrial cancer patients. We have examined the patients with serous, clear cell and carcinosarcoma histology who did not exceed 50% of myometrial invasion and evaluated the rates of metastasis to omentum, adnexa and lymph nodes in these patients. We have combined patients from two gynecological oncology centers to perform a larger study.

According to the results of the study, the rates of extra-uterine metastases in serous, clear cell and carcinosarcoma histological subgroups were not low. Omental metastasis rates were found to be 11-17%. Clear cell and carcinosarcoma subtypes had increased risk for omental metastasis. Interestingly, the rates of nodal metastases in these histological types were lower than serous type (Fig. 1). While retroperitoneal metastasis is more common in patients

with serous adenocarcinoma, clear cell and carcinosarcoma types might be more prone to omental spread (Fig. 1). In our study, myometrial invasion was less than one half in all patients, but the overall omental metastasis rate was 12.9%. However, in patients with non-endometrioid histology there is no consensus whether omentectomy should be a part of staging surgery. The ESMO-ESGO-ESTRO (European Society for Radiotherapy Oncology and European Society of Gynecological Oncology) group recommends omentectomy for serous histology, but not necessarily required for carcinosarcoma and clear cell adenocarcinoma.^[10] The National Comprehensive Cancer Network (NCCN) guideline supports that all of the non-endometrioid types are at high risk and that the omentectomy is part of the staging surgery.^[11] According to the study of Kaban et al., all patients with non-endometrioid type omentectomy were proposed.^[12] It seems reasonable that omentectomy is part of the staging surgery in non-endometrioid histologies.

Is re-operation necessary for staging surgery in non-endometrioid histology that has been detected incidentally? Inconsistency between the biopsy and the final pathology is possible.^[13-15] When incidentally non-endometrioid histology is detected, there are no clear recommendations in the management. Reoperation for staging may be considered in these patients according to the results of the study because omental metastasis rate was 11-17% (stage IV) and nodal metastasis rate was 4-12%. Differently, in a study conducted by Peled et al.,^[16] it is indicated that the survival rate was not different in those who had omentectomy or not in patients with serous endometrial carcinoma and reoperation was not recommended. However, reoperation may be useful for the detection of the stage and for a more appropriate adjuvant treatment plan. In another result of the study, it can be accepted whether the presence of adnexal metastasis as a criterion for re-operation decision for omentectomy if only hysterectomy and salpingo oophorectomy were performed. According to present study, the presence of adnexal metastasis for the prediction of omentum metastasis was a significant indicator in comparative analysis. In the absence of adnexal metastasis, the rate of omentum metastasis was 8%, while the presence of adnexal metastasis was 47% ($p=0.001$) (Table 2).

In this study we have evaluated patients with non-endometrioid endometrium carcinoma in terms of extra-uterine metastasis. Nonendometrioid histology accounts for 10-15% of endometrium cancers.^[17] The data was collected from only two centers over a 10-year period. This was a limitation of this study, so larger studies are needed. The fact that pathological examinations of preperats have not been reevaluated for study can be seen as another limitation.

In conclusion, according to the study, in non-endometrioid EC, the risk of extra-uterine metastases is not low even in early stages. If these histological types are detected by endometrial biopsy prior to surgery or incidentally after surgery, staging surgery including omentectomy should be planned.

Disclosures

Ethics Committee Approval: Ethical committee approval form was obtained from the Ethics Committee of Istanbul University (date: 9/3/2018 decision no: 05).

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