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ORIGINAL ARTICLE

Synchronous Endometrial and Ovarian Carcinomas; Correlation of Clinicopathological Parameters with Recurrence and Survival

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Abstract

Introduction: We aimed to determine the possible clinicopathological factors that might affect recurrence and survival in synchronous malignancy of the endometrium and ovary without discriminating the presence of two independent primary tumors or metastasis.

Methods: Patients who were admitted with the diagnosis of synchronous endometrial and ovarian cancer between 2000 and 2015 were reviewed retrospectively.

Results: Recurrence occurred in 12 (48%) patients. The mean duration of recurrence was 23.7 months. There is a significant relationship between presence of lenfovascular invasion), involvement of lymph node, spread to non-ovarian, and non-endometrial pelvic organs or beyond and the increase recurrence risk in the synchronous endometrial and ovarian cancer. The conditions involving the increased diameter of tumor in the endometrium and bilateral ovarian involvement are related with decreased survival. Besides, presence of endometrioid type ovarian tumor and absence of endometrial myometrial invasion are related with increased survival.

Discussion and Conclusion: Variables such as endometrial tumor diameter, myometrial invasion, endo/non endo type of ovarian tumor and presence of bilateral tumor were found to be effective on survival, variables such as lymphovascular invasion, lymph node involvement, and pelvic spread were effective on recurrence.

Keywords: Endometrium cancer; ovarian cancer; recurrence; synchronous; survival.

The synchronous malignancy of the endometrium and ovary is not a rare condition. It comprises 3–5% of endometrial cancers and 2–10% of ovarian cancers[1,2]. As these tumors might be two independent primary tumors, they might also be primary endometrial cancer with metastases to ovary or primary ovarian cancer with metastases to endometrium. The approach to the patient, treatment and prognosis are closely associated with the presence of which of these conditions. Two independent primary ovarian and endometrium tumors are considered have a good

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prognosis and do not require an aggressive treatment at the early stage than those with metastasis[3]. Although several pathological criteria have been detected, and clinical, molecular and immunohistochemical studies have been performed for an accurate differentiation, challenges are still present[4-7]. Since the prominence of molecular and genetic markers are not known exactly, nowadays, pathological criteria are still the most significant parameters in the diagnosis; however, the implementation of current criteria is not always easy[8,9].

In the present study, we experienced to determine the possible clinicopathological factors that might affect recurrence and survival in synchronous malignancy of the endometrium and ovary without discriminating the presence of two independent primary tumors or metastasis.

Materials and Methods

Our hospital is a maternity and pediatric hospital. Patients who were admitted to our hospital with the diagnosis of synchronous endometrial and ovarian cancer between 2000 and 2015 were reviewed retrospectively. During this period, a total of 510 endometrial cancers were diagnosed in our hospital. Our synchronous tumors are 36 and account for 7% of endometrial cancers. This is consistent with the literature. The ovarian cancers diagnosed in our hospital during this period were 395 and 36 synchronous tumors accounted for 9% of all ovarian cancers. Furthermore, this is consistent with the literature. Those with metastasis to endometrium and ovarian from another organ and those not having treatment or discontinued follow-up were excluded from the study. Due to lack of contact information and loss of follow-up, the data of 11 patients could not be accessed and 25 cases were included in the study. Follow-up was performed in months. The data about the clinicopathological examinations were collected by chart reviews.

All patients underwent a total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic, and paraaortic lymphadenectomy and omentectomy. All the sample slides were re-examined with light microscopy by the same pathologist. Age and menopausal conditions of the patients were evaluated as clinical data, and tumor diameter, bilateral ovarian involvement, histopathological type of ovarian and endometrial tumors (endometrioid/endometrioid, endometrioid/non-endometrioid, and non-endometrioid/non-endometrioid), tumor grade of endometrial and ovarian tumor, the presence and depth of endometrial myometrial invasion, lymphovascular invasion (LVI), involvement of lymph node, spread to pelvis and beyond the pelvis (those spread to non-ovarian and non-endometrial pelvic organs or beyond) and the presence of precursor lesion (endometriosis for ovary and atypical complex hyperplasia for endometrium) were evaluated as pathological criteria.

Patients were followed up for at least 12 months. Those having follow-up period of <12 months were considered lost to follow-up, unless recurrence occurred within this period.

Statistical Package for the Social Sciences (SPSS; Version 20.0, Chicago, IL, USA) was used for statistical analyses. Descriptive statistics were presented as counts and percentages for categorical data. The relationship between the categorical variables was examined using the Chi-square test and Fisher Exact Test. Results were evaluated with a confidence interval of 95%, and $p<0.05/p<0.01/p<0.1$. Log-rank test was used for the comparison of samples nonparametically. Cox regression analysis was used to determine the variables affecting survival and recurrence. Kaplan–Meier analysis was performed to determine the category-based differences of the variables effective in Cox regression.

Results

Thirty-six synchronous endometrial and ovarian cancers were present. A total of 25 patients were included in the study. The mean follow-up period was 40 months (range 12–122 months). Recurrence occurred in 12 (48%) patients. The number of surviving patients was thirteen and the number of patients who died was 12. The mean duration of recurrence was 23.7 months. The median of survival time was 22 months (range 3–104 months). The median age at diagnosis was 50.9 years (range 36–77 years). Percentage distribution of some categorical parameters is given in Table 1.

The analysis of recurrence based on the clinicopathological data is shown in Table 2.

Cox regression was used to determine whether all variables such as age, menopause, endometrial tumor diameter, ovarian tumor diameter, bilateral ovarian involvement, endometrioid or non-endometrioid types (endo/non-endo) for each endometrium tumor and ovarian tumor, endometrium tumor grade, ovarian tumor grade, myometrial invasion, lymphovascular invasion, lymph node involvement, spread to the pelvis and beyond, precursor lesions in the endometrium and ovary, were effective as a result of survival and recurrence. Cox regression was elaborated by Kaplan–Meier difference analysis for categorical variables affecting survival.

Variables of endometrial tumor diameter, myometrial inva-

Table 1. Percentage distribution of categorical parameters

	n	%
Menopause		
-	13	36.1
+	23	63.9
Edometrial tumor		
Endo	23	63.9
Non-endo	13	36.1
Ovarian tumor		
Endo	17	47.2
Non-endo	19	52.8
Bilateral status		
Unilateral	23	71.9
Bileteral	9	28.1
Myometrial invasion		
-	14	38.9
+	22	61.1
Endometrial tumor grade		
Low	19	52.8
High	17	47.2
Ovarian tumor grade		
Low	15	44.1
High	19	55.9
Lymph node involvement		
-	23	63.9
+	13	36.1
Pelvic spread		
-	21	58.3
+	15	41.7
Lymphovascular invasion		
-	21	58.3
+	15	41.7

Table 2. Recurrence analysis based on clinicopathological features

Clinicopathological parameters (n=25)	Recurrence n=12 (%)	Non-recurrence n=13 (%)	p
Age (year)			
<50	5 (42)	8 (64)	0.320[1]
>50	7 (58)	5 (36)	
Menopausal status			
Var	10 (84)	8 (64)	0.225[1]
Yok	2 (16)	5 (36)	
Endometrium tumor size			
<5	4 (33)	12 (92)	0.002**[1]
>5	8 (67)	1 (8)	
Ovarian tumor size			
<5	7 (58)	1 (8)	0.007**[1]
>5	5 (42)	12 (92)	
Bilateral ovarian involvement			
+	4 (33)	2 (15)	0.294[1]
-	8 (67)	11 (85)	
Histologic type			
Endo/Endo	7 (58)	6 (46)	0.185[2]
Endo/Non-endo	1 (8)	5 (39)	
Non-endo/Non-endo	4 (34)	2 (15)	
Endometrium tumor grade			
Low	3 (25)	11 (85)	0.003**[1]
High	9 (75)	2 (15)	
Ovarian tumor grade			
Low	4 (33)	9 (70)	0.073[1]
High	8 (67)	4 (30)	
Myometrial invasion			
-	3 (25)	6 (46)	0.271[1]
+	9 (75)	7 (64)	
Lenfovascular invasion			
+	7 (58)	2 (15)	0.025*[1]
-	5 (42)	11 (85)	
Lymph node involvement			
+	5 (42)	1 (8)	0.047*[1]
-	7 (58)	12 (92)	
Pelvic and beyond involvement			
+	6 (50)	2 (15)	0.064[1]
-	6 (50)	11 (85)	
Endometriozis			
+	1 (8)	5 (38)	0.078[1]
-	11 (92)	8 (62)	
Complex hyperplasia with atypia			
+	2 (16)	8 (62)	0.022*[1]
-	10 (84)	5 (38)	

[1]Fischer Exact Test p value *p<0.05 **p<0.01 [2]Chi-square test p-value.

sion, endo/non-endo type of ovarian tumor, and presence of bilateral tumor were found to be effective on survival (Table 3).

- One unit increase in endometrial tumor diameter decreases 1.62 (1.0162; 2.58) times survival time
- Presence of endo type ovarian tumor increases 10.68 (1.36; 86.33) times survival time compared to non-endo type. According to this, it is understood that the life expectancy of the patients in endo type ovarian tumor (73.19±10.02) is higher than non-endo group patients (36.15±6.06). Comparisons of endo and non-endo groups are given in Table 4.
- The absence of myometrial invasion increases the 7.56 (0.75; 75.45) times survival time.
- Bilateral state of the ovarian tumor reduces the 10.9 (0.85; 142.85) times survival time compared to the unilateral state.
- Among the variables, lymphovascular invasion, lymph node involvement, and pelvic spread were found to be

Table 3. Variables affecting survival after multivariable cox regression analysis

Variables	B	SE	Sig.	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Endometrium tumor diameter	–0.483	0.238	0.042**	0.617	0.387	0.984
Myometrial invasion	2.024	1.173	0.085*	7.567	0.759	75.456
Ovarian tumor type	2.368	1.066	0.026**	10.680	1.321	86.332
Bilateral involvement	–2.399	1.303	0.066*	0.091	0.007	1.168

***p<0.01 **p<0.05 *p<0.1.

Table 4. Survival time comparisons of endo and non-endo type ovarian tumors

Ovarian tumor	Mean				p[1]
	Estimate	Std. Error	95% Confidence Interval		
			Lower Bound	Upper Bound	
Endo	73.192	10.020	53.554	92.831	0.025*
Non-endo	36.159	6.061	24.279	48.040	
Overall	59.852	8.386	43.415	76.288	

***p<0.01 **p<0.05 *p<0.1 1: Log-rank test p-value.

effective on recurrence (Tables 5 and 6).

- In cases of LVI, 7.10 (1.71; 29.36) times risk of recurrence was detected compared to absence of LVI. The mean recurrence time was higher in patients without lymphovascular invasion (88.09±13.35) than in patients with lymphovascular invasion (27.37±4.42).
- In case of lymph node involvement, 6.30 (1.65; 23.98) times recurrence risk was detected. The mean duration of recurrence was higher in patients without lymph node involvement (84.19±24.61) than in patients with lymph node involvement.
- In the case of pelvic spread, 4.18 (1.24; 14.06) times recurrence risk has been identified

All patients underwent surgery and received chemotherapy. Three patients received both chemotherapy and radiotherapy.

Discussion

The diagnosis of synchronous endometrial and ovarian cancers is a difficult situation for pathologist, and patient management is challenging for the clinician[10]. They may represent as an independent primary tumor or a metastatic disease. The treatment is contradictive, as well as independent primary tumors have a good prognosis and surgical therapy may be sufficient in the early period of the disease[4,11]. Adjuvant therapy might be essential for metastatic tumors. Independent primary tumors are classified as FIGO Stage IIIA endometrial cancer or FIGO Stage IIA ovarian cancer, and they might be over-treated, or treatment might be interrupted at the opposite situation. Several pathological criteria have been described for this discrimination; histologic type, tumor grade, presence and extent of myometrial invasion, vascular invasion, ovar-

Table 5. Variables affecting recurrence after multivariable cox regression analysis

Variables	B	SE	p	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Lenfovascular invasion	1.961	0.724	0.007***	7.103	1.719	29.360
Lymph node involvement	1.842	0.681	0.007***	6.308	1.659	23.987
Pelvic and beyond involvement	1.431	0.619	0.021**	4.183	1.244	14.062

***p<0.01 **p<0.05 *p<0.1.

Table 6. Variables affecting recurrence time

Variables	over_TM	Mean				p[1]
		Estimate	Std. Error	95% Confidence Interval		
				Lower Bound	Upper Bound	
Lenfovascular invasion						
	(-)	88.093	13.353	61.921	114.266	0.002**
	(+)	27.375	4.423	18.705	36.045	
	Overall	69.288	11.305	47.130	91.446	
Lymph node involvement						
	(-)	84.190	12.926	58.854	109.525	0.002**
	(+)	24.611	5.618	13.601	35.621	
	Overall	69.288	11.305	47.130	91.446	
Pelvic and beyond involvement						
	(-)	87.172	13.766	60.190	114.154	0.012
	(+)	32.775	7.474	18.126	47.424	
	Overall	69.288	11.305	47.130	91.446	

***p<0.01 **p<0.05 *p<0.1 Log-rank test p value.

ian tumor size, pattern of ovarian involvement, presence of tumor in the fallopian tube, and presence/absence of precursor lesions (ovarian endometriosis and complex hyperplasia with atypia)[7,10]. These parameters might be engaged in many cases, and diagnosis is difficult when some of them are detected and some are not[4]. Same histological tumor type should be considered as a metastatic disease; however, there might be two independent primary tumors, as well. The reverse is also possible a metastatic condition from one to another might be present due to tumor differentiation or clonal heterogeneity, although two independent cancers have different histological types. Several molecular analyses and immunohistochemical studies have been performed for discrimination in addition to pathological criteria; DNA flow cytometry, loss of heterozygosity on chromosome, X chromosome instability, DNA mismatch repair protein expression analysis, and immunohistochemical analysis of HER-2/neu, p53, ki67, ER, PR, and bcl-2[6,9]. A consensus could not be reached in the end and pathological criteria are still considered as the most basic factor for differentiation. As it has been aimed for determining the relapse, prognosis and treatment of disease, we evaluated the association of clinicopathological parameters with recurrence and survival.

Various studies showed that the prognosis of synchronous endometrial and ovarian cancers was better in patients under the age of 50 years than those above 50 years of age. This condition might be associated with the incidence of synchronous two independent primary tumors in younger ages and its good prognosis than others, and the incidence of metastatic tumors in above the age of 60 years[4,12,13]. Bese et al. [12] found advanced age as an important risk factor for recurrence. Our study results were complied with this information and the mean age of patients was found as 50.9 years (the mean ages of groups with and without recurrence: 54 years and 50.9 years, respectively; p=0.320). Similarly, being at postmenopausal period has been also considered as an important risk factor for recurrence[12]. In our study, of the 12 patients with recurrence, 10 were postmenopausal. Although, it is not statistically significant, advanced age and postmenopausal condition are associated with the tendency to recurrence. No effect of age and menopause status on overall survival was detected.

Among the pathological parameters, there is limited number of studies related to tumor size. The small size of ovary and tumor was associated with metastasis from endometrium to ovary[14].

In our study, we detected that increased tumor diameter in the endometrium was associated with decreased survival (0.042). Of the 8 ovarian tumors with the diameter of <5 cm, 7 were in the recurrence group. Although not statistically significant, decrease in ovarian tumor size was associated with decreased risk of recurrence. This may be related to metastasis from the endometrium to ovary.

Bilateral ovarian involvement was associated with metastasis from endometrium[8]. In certain studies, the rate of bilateral ovarian involvement is in substantial degree in

synchronous primary tumors[4]. In our study, we reported that bilateral ovarian involvement was associated with decreased survival. And this suggests that bilateral involvement may be related to metastasis. Bilateral ovarian involvement had no effect on the recurrence.

There are various studies involving the association of tumor type and similarity with prognosis[15-17]. The common opinion is that the most prevalent type in synchronous tumors is endometrioid adenocarcinoma, and in general, endometrioid is a low grade and early stage tumor found in both localization in synchronous two primary tumors, and they have better prognosis than the metastatic tumors. A few of researchers explained this condition with being at early stage and low-grade, and some of them considered the association of endometrioid type with good prognosis. Another opinion was that histopathological type did not affect survival[15,18]. In the present study, most of the patients (52%) had endometrioid type tumor in both localization. Endometrioid type of ovarian tumor was found to be significant for increased survival (0.025). Of the 13 patients in endo/endo group, seven patients were in recurrence group. Only one patient with serous tumor was in the recurrence group only in endo/non-endo group. Of the 6 patients in non-endo/non-endo group, 4 were in the recurrence group, and all of them were serous/serous. Although tumor type does not have a significant relationship with recurrence, it might be concluded that the presence of serous tumors in one or both localizations is associated with recurrence tendency.

The presence of endometrial and ovarian tumor with low histologic grade is associated with good prognosis[13,19]. However, in certain studies, it was emphasized that the grade of endometrial tumor was more effective in recurrence and prognosis than the ovary[12].

In our study, of the 11 patients with high grade endometrial tumor, 9 were in the recurrence group; of the 12 patients with high grade ovarian tumor, and 8 were in recurrence group. Although high grade tumor in endometrium and ovary might cause recurrence, tumor grade had no effect on overall survival and recurrence.

Deep myometrial invasion was identified with metastasis from the endometrium to the ovary[14]. In the study of Zaino et al., [20] it was stated that deep myometrial invasion had a significant effect on bad prognosis, and while 77% of patients with deep myometrial invasion were associated with recurrence, recurrence was present only in 17% of patients with superficial invasion. In our study, of the 12 patients with recurrence, 9 had myometrial invasion and deep invasion was present in 5 of them. The presence of myometrial invasion has a tendency to recurrence but is not statistically significant. Furthermore, it is associated with decreased survival (p=0.085).

LVI is commented on behalf of metastatic disease rather than two independent primary tumors[11]. In previous studies, a strong correlation was detected among LVI and recurrence, and it was accepted as a bad prognostic factor[11]. In our study, of the 9 patients with LVI, 7 were in the recurrence group. The association between LVI and recurrence is significant (p=0.007).

Involvement of the lymph nodes is names as "advanced stage" for synchronous endometrial and ovarian cancers and it has been accepted as a bad prognostic factor. In our study, of the 6 patients with lymph node involvement, 5 were in the recurrence group and lymph node involvement showed a significant correlation with recurrence risk, in line with previous studies (p=0.007).

In the same way, the spread to pelvis and beyond the pelvis, outside of the endometrium and ovary, are classified as "advanced stage" tumors for endometrium and ovary, and closely associated with bad prognosis[16]. In line with these studies, 6 of 8 patients not limited to ovary and endometrium were in the recurrence group. The presence of spread is associated with recurrence tendency (p=0.021).

Among the precursor lesions, ovarian endometriosis is identified in about 30% of synchronous endometrial and ovarian cancers, especially of endometrioid type[5]. The etiology of synchronous endometrial and ovarian cancers is contradictive, the theory of "secondary mullerian system" proposed that the epithelia of cervix, uterus, fallopian tubes, ovaries, and peritoneal surface had shared molecular receptors responding to carcinogenic stimulus leading to the development of multiple primary malignancies synchronously[2]. Endometriotic implants may undergo direct malignant transformation or the cancer and endometriosis have in common many environmental, immunological, hormonal, or genetic predisposing factors[2]. Endometriosis is generally associated with low-stage and good survival in synchronous ovarian and endometrial tumors[21,16]. In the present study, endometriosis was detected in six patients and only one patient was in group with recurrence. Even there was no significant correlation, it was a remarkable result (p=0.078). Atypical complex hyperplasia, a precursor lesion, had a close association with synchronous tumors, and especially with low-stage and good survival[11]. In the present study, of the eight patients with hyperplasia, only two were in the recurrence group. Although there was a

relationship between precursor lesions and absence of recurrence, there was no significant association between survival and recurrence.

Conclusion

Variables such as endometrial tumor diameter, myometrial invasion, endo/non-endo type of ovarian tumor and presence of bilateral tumor were found to be effective on survival, variables such as lymphovascular invasion, lymph node involvement, and pelvic spread were effective on recurrence.

Further studies involving a scoring system based on enriched clinicopathological parameters can overcome the discussion of primary tumor or metastases in synchronous tumors and lead to new approaches in patient management and treatment.

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