Coexisting Primary Cancers of Endometrium and Ovary: Experience of Single Institution

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ABSTRACT

Synchronous primary cancers of the endometrium and ovary (SEOC) occur in approximately 10% of all women with ovarian cancer and 5% of all women with endometrial cancer. Diagnosis of these tumors as independent primaries or metastases is necessary for appropriate staging and treatment. We aimed to demonstrate the clinic-pathological characteristics and prognosis of patients diagnosed as SEOC. Clinico-pathological data of cases with SEOC were retrieved from the computerized database of Etlik Zubeyde Hanim Women's Health and Research Hospital. Twenty-six patients with SEOC who underwent comprehensive surgical staging between 1998 and 2014 were included in study. Mean age at diagnosis of women with primary SEOC in our study was 50.9. Median follow up was 86.5 months and the 10 year overall survival (OS) rates were 86.0% for patients with SEOC. Among the variables only omental involvement independently affected OS (p= 0.008). Most of the tumors were well-differentiated, early stage and of endometrioid cell type. In this study we showed that women with SEOC was often young and mostly have an excellent prognosis.

Keywords: Endometrial Cancer, Ovarian Cancer, Synchronous Tumors, Survival

ÖZET

Endometrium ve Overin Eşzamanlı Primer Kanserleri: Tek Merkezin Sonuçları

Endometrium ve overin senkron gelişen primer tümorleri (SEOT); tüm over kanserli kadınların %10'unda, endometrium kanserli olguların ise %5'inde görülmektedir. Uygun evreleme ve tedavi için olguların bağımsız primer kanser veya metastatik olup olmadıkları ortaya konmalıdır. Çalışmamızda SEOT tanısı alan olguların klinik ve patolojik özellikleri ile prognozlarının ortaya konması amaçlanmıştır. Hastaların bilgileri Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi bilgisayar kayıtlarından çıkarıldı. 1998 ile 2014 yılları arasında cerrahi evrelendirme yapılmış ve SEOT tanısı almış, toplam yirmialtı hasta çalışmaya dahil edildi. Tanı esnasında ortalama yaş 50.9 idi. Medyan takip süresi 86.5 ay ve 10 yıllık sağkalım oranı %86 olarak bulundu. Prognostik değişkenler içinde, yalnız omental tutulumun genel sağkalımı bağımsız olarak etkilediği görüldü (p= 0.008). Tümörlerin büyük çoğunluğu iyi diferansiye, erken evre ve endometrioid tipte idi. Sonuç olarak SEOT tanısı alan kadınların çoğunlukla genç yaşta oldukları ve prognozlarının yalnız başına over kanserlerine göre belirgin olarak daha iyi olduğu ortaya konmuştur.

Anahtar Kelimeler: Endometrium Kanseri, Over Kanseri, Senkron Tümörler, Sağkalım

INTRODUCTION

It has been shown that primary cancer can occur in the female reproductive organs simultaneously, especially with endometrial and ovarian cancers. The coexistence of synchronous multiple primary neoplasms are clinically very important due to prognostic and therapeutic considerations. Synchronous primary cancers of the endometrium and ovary (SEOC) occur in approximately 10% of all women with ovarian cancer and 5% of all women with endometrial cancer.[1,2] SEOC account for 50-70% of all synchronous female genital tract malignancies.[3] This phenomenon is almost unique to the female genital tract. Accurate diagnosis of these tumors as independent primaries or metastases is necessary for appropriate staging and treatment. Pathological criteria for distinguishing synchronous tumours from metastases were first documented by Ulbright and Roth, and subsequently detailed by Scully et al.[4,5] Molecular profiling of the tumors in the endometrium and ovary can improve the detection of independent primary tumors.[6]

Our major aim in this study was to show the clinical-pathological characteristics and prognosis of patients diagnosed as SEOC.

PATIENTS AND METHODS

After obtaining approval from the Institutional Review Board at Etlik Zubeyde Hanim Women's Health and Research Hospital study population was identified through a search of the gynecologic oncology and pathology database. Patients were included in the study based on histopathologic diagnosis by a gynecologic pathologist at our institution. Twenty-six patients with SEOC who underwent comprehensive surgical staging between 1998 and 2014 were included in study. Patients underwent standard surgical approach including total or radical abdominal hysterectomy, bilateral salpingo-oophorectomy, systemic bilateral pelvic and para-aortic lymphadenectomy, omentectomy, and appendectomy. All patients had their primary evaluation and surgical staging procedure performed at our hospital and were staged using FIGO (International Federation of Gynecology and Obstetrics) 2009 surgical criteria for endometrial and ovarian cancer. Adjuvant treatment was offered based on the individual patient's needs according to surgical staging and our protocols. Information regarding to age at diagnosis, personal or family history of cancer, time of operation, clinical presentation, laboratory values and modality of treatment were obtained from medical records. Pathologic information such as histology, tumor size, bilaterality, FIGO grade, depth of myometrial invasion, lymphovascular space invasion (LVSI), and number of lymph node were collected from surgical pathology reports. Histopathological evaluation differentiating synchronous carcinoma from metastatic carcinoma was based on the World Health Organization criteria[7] and the criteria of Scully et al.[5] and diagnosis was made simultaneously. Patient follow-up was started when the first cancer diagnosis was made and terminated when the patient had died or on the last contact at our outpatient clinics or in telephone (December 2014). SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for the data management and statistical analysis. Kaplan-Meier method was used for the assessment of survival outcomes.

RESULTS

Twenty-six patients with SEOC included in study. Mean age of patients at the time of diagnosis was 50.9 ± 9 years. Most common presenting symptoms of patients were abdominal/pelvic mass (n= 9; 34.6%), postmenopausal bleeding (n= 8; 30.8%) and menorrhagia (n= 6; 23.1%). Three patients had both complaint of pelvic mass and menorrhagia. None of the patients had family history of colon, gastric or breast cancer and no secondary malignancy was detected during the follow up period. Before the operation eighteen patients were diagnosed as endometrioid carcinoma of the uterus according to probe curettage. Mean CA-125 levels were 137.2 ± 156.3 mU/L. All patients underwent total abdominal hysterectomy bilateral salpingo-oophorectomy, omentectomy and systemic bilateral pelvic and para-aortic lymphadenectomy and maximal debulking was achieved when patients had been found intra-abdominal lesions including ascites, omental, nodal, and peritoneal disease. Appendectomy was performed in thirteen (50%)

Table 1. Characteristics of endometrial tumor of SEOC (n= 26).

	Number	%
Histology		
Endometrioid	24	92.3
Mucinous	2	7.7
Stage		
1a	18	69.2
1b	5	19.2
2	2	7.7
3c	2	3.8
Grade		
1	18	69.2
2	7	26.9
3	1	3.8
Myometrial invasion		
<1/2	18	69.2
>1/2	8	30.2
Cervical involvement		
Yes	2	7.7
No	24	92.3
LVSI*		
Yes	4	15.4
No	22	84.6
1		
Largest Diameter		
≤ 2 cm	12	46.2
>2 cm	13	50
Unknown	1	3.8

*: Lymphovascular space involvement

Table 2. Characteristics of ovarian tumor of SEOC (n= 26)

	Number	%
Histology		
Endomerioid	19	73.1
Serous	2	7.7
Granulosa	2	7.7
Mixt (endometrioid+clear)	1	3.8
Mucinous	1	3.8
Undifferentiated	1	3.8
Stage		
1a	11	42.3
1b	1	3.8
1c	6	23.1
2a	1	3.8
3a	1	3.8
3b	1	3.8
3c	5	19.2
Grade		
1	15	57.7
2	4	15.4
3	3	11.5
Unspecified	4	
15.4		
Largest diameter		
≤ 10 cm	18	69.2
≥ 10 cm	5	19.2
Unknown	3	11.6
Peritoneal cytology		
Positive	5	19.2
Negative	21	80.8
Omental involvement		
Yes	5	19.2
No	21	80.8
Lyphnode involvement		
Yes	3	11.5
No	23	88.5

patients. Two patients with cervical involvement received radical hysterectomy during the operation according to frozen pathology result of specimen. Mean number of total lymph node extracted during the surgery was 61.6 ± 25. Synchronous independent primary tumors were detected simultaneously in all cases according to Scully's criteria. The histopathological characteristics of the endometrial and ovarian tumors of SEOC are listed in Table 1 and Table 2 respectively. Twenty-four patients had endometrioid carcinoma while 2 patients had mucinous carcinoma of uterus. One of the 2 patients with mucinous carcinoma of uterus had endometrioid and the other one had granulosa cell carcinoma of ovary. Eighteen patients (69.2%) had endometrioid carcinoma at both uterus and ovary. Remaining 6 patients had less common ovarian tumor histology (serous, granulosa, mixt endometrioid+ clear, mucinous, undifferentiated). Eight patients had deep myometrial invasion (>1/2) and four patients had LVSI. Fifteen patients had FIGO stage I endometrial and ovarian carcinomas (Table 3). Also twelve patients (46.2 %) had FIGO grade I endometrial and ovarian tumors. Seventeen patients (65.4 %) received adjuvant therapy. Of these, 13 had chemotherapy (76.5%), 3 had chemotherapy plus radiotherapy (2 cuff and 1 pelvic, 17.6%) and

Table 3. FIGO stages of ovarian and uterine tumors of SEOC

	Ovarian stage						
Endometrial stage	**1a**	**1b**	**1c**	**2a**	**3a**	**3b**	**3c**
1a	9	1	1	1	1	1	4
1b	2	0	2	0	0	0	1
2	0	0	2	0	0	0	0
3c	0	0	1	0	0	0	0

1 had only cuff radiotherapy (5.9 %).

Median follow up was 86.5 months and the 10-year overall survival (OS) rates were 86.0% for patients with SEOC.(Figure 1) One patient died on the twentieth day after operation due to pulmonary embolism and two patients died due to cancer related diseases during the follow up period. Three patients experienced a recurrence of tumor. We were unable to compare overall survival for the different endometrial and ovarian pathological groups because of limited subgroup sample size. There were no statistically significant differences in survival by endometrial cancer stage, grade, depth of myometrial invasion or presence of LVSI. It was also found no significant differences in survival related to ovarian cancer stage, grade, baseline Ca 125 level, lymph node metastasis, number of lymph node, cytology or adjuvant treatment. Our ability to detect differences in survival based on these prognostic factors might be limited by the small sample size. It was showed that only omental involvement independently affected OS (p= 0.008).

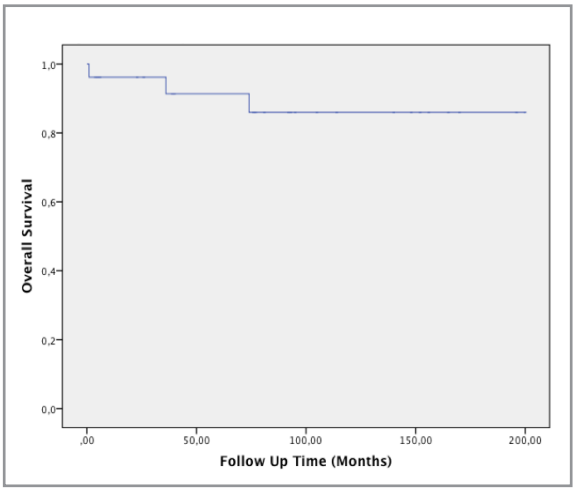

Figure 1. Overall Survival of Synchronous Endometrial and Ovarian Cancer

DISCUSSION

Primary synchronous cancers in the female genital tract occur in approximately 1% to 2% of gynecological cancer. Patients with simultaneously detected endometrial and ovarian malignancies constitute majority of them.[3,8] Women with synchronous primary cancers of the endometrium and ovary are different from the women with endometrial or ovarian cancer alone. The foremost problem in studying this population of women is making the correct diagnosis of independent primary tumors for appropriate management. Pathologists including Scully et al. have revealed histologic criteria to aid pathologists when evaluating these tumors. In our study diagnoses of SEOC were made according to these criteria that still seems to offer great benefit until the strict molecular or genetic alterations are found for the definitive diagnosis. In the future some molecular profiles and genetic changes that present in these tumor may improve the distinction of independent primary tumors.[9]

Mean age at diagnosis of women with primary SEOC in our study was 50.9. In contrast, women who develop endometrial or ovarian cancer alone are generally postmenopausal and in the sixth or seventh decade of life.[8] In previous studies reported age of patients with SEOC ranged between 41 and 52 years.[10] It was found that prominent presenting symptom was abnormal uterine bleeding (65.4%) in patients with synchronous tumors, therefore most of the patients with SEOC diagnosed primar-

ily as endometrial cancer (n= 18; 69.2%) in study cohort. Careful pre- and intra-operative evaluation of both ovaries is mandatory for making an appropriate treatment plan before surgery, especially in young patients with a wish to preserve fertility. Determination of initial CA-125 level before the operation has shown to be helpful both in the evaluation of adnexal mass and for patients with endometrial cancer.[11] Although baseline mean CA-125 level (137.2 mU/L) of our patients was higher than normal, it was still lower than the mean values which found in metastatic endometrial(to ovary) or ovarian carcinoma(to endometrium) alone (308.4 and 1835 mU/L respectively) in the study of Broeders FM and et al.[12]

Ovarian cancer, which often presents with nonspecific symptoms, is more commonly diagnosed at an advanced stage (75-85% stage III/IV).[13] In our series of patients, 69.2% of them had FIGO stage I ovarian cancer at the time of diagnosis. The earlier detection of ovarian cancer in this study was likely due to early symptoms (i.e., abnormal vaginal bleeding) related to concurrent endometrial cancer. Eighteen cases (69.2%) showed endometrioid cell-type tumor at both endometrium and ovary. Also most of the patients with SEOC had FIGO grade I endometrial and ovarian tumors (69.2% and 57.7% respectively). Since majority of the patients with SEOC had early stage and low-grade tumors, 10-years OS approaches 90% in our study. This result correlates with the Gynecologic Oncology Group's study finding which showed that 10- year survival of SEOC was 80%.[1] Possible explanation for the relatively good prognosis could be the accurate examination of women when one tumor detected. Women older than 50 years of age seemed to have better 5-year disease free survival than younger women (72.9% and 90.9% respectively), but the difference was not significant (p= 0.332). Although familial cancer syndromes are often involved in the pathogenesis of synchronous cancers, in our study there was no hereditary cancer syndrome. We could not find any prognostic factor other than omental involvement that effects the survival. It was independent prognostic factor in women with SEOC. The main limitation of current study is small sample size, retrospective character of study and absence of central pathologic review.

In summary, in this retrospective clinicopathologic study of 26 patients, it was found that women with SEOC mostly have an excellent prognosis. Only three patients suffered a recurrence during the median follow up period of more than 7 years. Most of the tumors were well-differentiated, early stage and of endometrioid cell type. Since patients with SEOC are often young and usually first presenting symptom is abnormal uterine bleeding, preoperative workup should be complete to make appropriate treatment plan.

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