Synchronous tumors of the female genital tract: A 20-year experience in a single center

Synchroniczne nowotwory narządu płciowego kobiety: 20-letnie doświadczenie jednego ośrodka

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Abstract

Objective: *To evaluate the clinicopathological characteristics and the clinical outcome of synchronous malignant neoplasms of the female reproductive tract.*

Material and Methods: *Patients who were operated and diagnosed with synchronous malignant tumor of the genital system (n=25) at the Dokuz Eylul University Department of Obstetrics and Gynecology, Gynecologic Oncology Unit between 1992 and 2012 were included into this study. Recurrent, metastatic and metachronously detected tumors were not included. Age at diagnosis, parity, menopausal status, hormone use, presenting sign or symptoms and the clinical outcomes were evaluated.*

Results: *20 of 25 patients had endometrial-ovarian cancer. The mean age at diagnosis was 53,6 years. The most common presenting symptom was abnormal uterine bleeding. The median follow-up duration for all patients was 69 months. Overall survival for all patients was 87 months and 81 months for patients with endometrial-ovarian cancer. 5-year survival rate was 73% for all patients and 68% for patients with endometrial-ovarian cancer.*

Conclusions: *Endometrial-ovarian cancer togetherness is the most common in synchronous gynecologic malignancies. They occur at a younger age and have more favorable prognosis than metastatic primary gynecologic tumors.*

Key words: **outcome** / **genital tracts** / **synchronous tumor** /

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Streszczenie

Cel pracy: *Celem pracy była patologiczna oraz kliniczna ocena synchronicznych nowotworów dróg rodnych.*

Materiał i metody: *Do badania włączono pacjentki, u których stwierdzono złośliwe synchroniczne nowotwory dróg rodnych (n=25) i które były z tego powodu leczone operacyjnie w Klinice Położnictwa i Ginekologii na Oddziale Onkologii Ginekologicznej Uniwersytetu „9 Eylul" w Izmirze (Turcja) w okresie od 1992 do 2012 roku. Pacjentki, u których stwierdzono guzy nawrotowe, przerzutowe synchroniczne bądź metasynchroniczne były wykluczone z badania. W pracy oceniono wiek pacjentek w momencie postawienia diagnozy, ich dzietność, status menopauzalny, ewentualną obecność endometriozy i stosowanie leków hormonalnych, jak również obecne objawy podmiotowe i przedmiotowe oraz wyniki kliniczne.*

Wyniki: *U 20 z 25 pacjentek stwierdzono współwystępowanie raka trzonu macicy i jajnika. Średnia wieku w momencie postawienia diagnozy wynosiła 53,6 lat. Najczęstszym objawem było zaś nieprawidłowe krwawienie z dróg rodnych. Średni czas obserwacji chorych wynosił 69 miesięcy. Całkowite przeżycie w badanej grupie wyniosło 87 miesięcy, natomiast u pacjentek, u których stwierdzono współwystępowanie raka trzonu macicy i jajnika wynosiło ono 81 miesięcy. Odsetek przeżyć pięcioletnich w całej grupie wynosił 73%, zaś w grupie chorych, u których stwierdzono współwystępowanie raka trzonu macicy i jajnika wynosiło ono odpowiednio 68%.*

Wnioski: *Wśród złośliwych synchronicznych nowotworów dróg rodnych współwystępowanie raka trzonu macicy i jajnika jest najczęstsze. Złośliwe nowotwory synchroniczne są stwierdzane we wcześniejszym wieku i mają korzystniejszą prognozę niż pierwotne nowotwory dróg rodnych dające przerzuty.*

Słowa kluczowe: **drogi rodne** / **wyniki** / **nowotwór synchroniczny** /

Introduction

Coexistence of more than one primary malignancy in the female genital tract is about 1-6% [1-3]. The most frequent synchronous gynecological neoplasms are ovarian and endometrial cancers. Synchronous primary cancers of the endometrium and ovary occur in approximately 10% of all women with ovarian cancer and 5% of all women with endometrial cancer [4].

The etiology of gynecologic synchronous malignancies is not clear; however it has been postulated that embryologically similar tissues of the female genital tract may develop synchronous neoplasms when simultaneously subjected to carcinogens or hormonal influences [5-6]. This phenomenon may explain the occurrence of synchronous tumors of similar or identical histology. But tumors with completely different histological subtypes may occur at the same time in the same patient. The infections such as human papilloma virus infection or the mutations such as those in Lynch Syndrome may also cause synchronous malignancies in the female genital tract.

It is critical in these tumors to differentiate the separate primary malignancies from the metastasis of one organ's tumor to the other. The clinicopathological characteristics to diagnose independent primary cancers were described in different studies [7-8]. The prognosis of synchronous tumors is also a matter of debate. Earlier studies suggested that women diagnosed with synchronous primary cancers have a better overall prognosis than women with cancers classified as single organ disease with metastasis [4, 9]

In this retrospective study, we aimed to put forward the clinical features of this rare type of gynecological tumors. We hypothesized that synchronous genital tumors occur at a younger age and have a better prognosis than metastatic tumors. We reviewed the records of patients with synchronous tumors of the female genital tract in the past two decades and presented the clinicopathological features as well as the prognosis of these tumors.

Materials and methods

Patients with synchronous genital neoplasms who were operated on and followed-up at Dokuz Eylul University Department of Obstetrics and Gynecology, Gynecologic Oncology Unit between 1992 and 2012 were included in this study. All specimens were examined macroscopically and microscopically by the same experienced gynecological pathologist at our institution. Recurrent, metastatic and metachronously detected tumors were not included. Only second or third primary neoplasms, which had been diagnosed concurrently with the primary neoplasm, discovered during the primary surgical procedure were included in this study. The diagnostic criteria for the synchronous tumors include either the detection of different histological subtypes or all of the following rules if the histological subtypes were similar: (*i*) both tumors confined to primary sites, (*ii*) no direct extension between tumors, (*iii*) no lymph-vascular tumor emboli, (*iv*) no or only superficial myometrial invasion, and (*v*) no distant metastasis [7, 8, 10, 11].

Complete staging procedure was performed for all the patients who had ovarian or tubal cancer. Radical hysterectomy and pelvic and paraaortic lymphadenectomy were performed for cervical cancer. Radical vulvectomy and bilateral inguinal lymphadenectomy was performed in vulvar cancer. Adjuvant therapy was given if it is indicated.

Demographic data including age at diagnosis, parity, menopausal status, hormone use, and the presenting sign or symptoms were recorded. Pathologic information related to histological subtype, grade and stage was recorded. Histological determination of the tumors was based on the World Health Organization (WHO) Committee classification of tumors and patients were staged in accordance with FIGO-1988 recommendations for ovarian cancer, FIGO-2009 recommendations for the endometrial, cervical and vulvar cancer. The tumors were re-staged according to the recommendations mentioned above if the patient was operated on before this date. Platin sensitivity was also examined in patients

with synchronous ovarian and endometrial cancer who had adjuvant chemotherapy. Follow-up durations and the time of recurrence if present were recorded in all patients. Follow-up intervals were determined up to the last available information regarding the clinical status of each patient. Survival time was measured in months from the time of diagnosis to the date of most recent follow-up or death.

The data were analyzed using SPSS 15.0 software (SPSS Inc., Chicago, IL, United States). Survival analyses were generated by Kaplan–Meier [12] and compared using the log-rank test. Continuous data were expressed as mean ± standard deviation (SD) or minimum/maximum levels. Categorical data were analyzed with chi square of Fisher's exact tests. A probability value of <0.05 represented statistical significance.

Results

There were 29 patients with synchronous female genital tract tumors operated between 1992 and 2012 in our department. 4 patients were lost to follow-up just after the operation**,** so 25 patients were included in the study. Of these patients, 80% had both ovarian and endometrial cancer. The distribution of patients according to the primary sites is presented in Table I.

The mean age at diagnosis was 53,6 years (range: 27-75 years). The median parity was 3 (range: 0-7 births), two patients were nulliparous. 20 of all patients (80%) were postmenopausal. None of them had received hormone replacement therapy.

The most common presenting symptom was abnormal uterine bleeding (48%). Pelvic pain, abdominal distention and the vulvar lesion were the other symptoms with the incidence of 28%, 20% and 4% respectively. The clinicopathological characteristics of the most common type of synchronous genital tumor**,** which was primary endometrial and ovarian cancer together, are presented in Table II.

There were five patients who had similar histology in both ovary and endometrium. Four of them had endometrioid adenocarcinoma and the fifth had clear cell adenocarcinoma.

The median follow-up duration for all patients was 69 months (range: 6-178 months). For all patients**,** overall survival (OS) was 87 months and disease free survival (DFS) was 71 months. 5-year survival rate was 73% and 5-year DFS rate was 64%.

Table I. Synchronous malignant neoplasm

Primary Site	n	%
Ovarian + endometrial	20	80
Ovarian + cervical	1	4
Ovarian + endometrial + cervical	2	8
Endometrial + tubal	1	4
Endometrial + vulvar	1	4
Total	**25**	**100**

Table II. Clinicopathological features of the synchronous primary endometrial and ovarian cancers.

Patient	Age (years)	Endometrial cancer		Ovarian cancer		Survival (months)	Last Status
		Histology	Stage/Grade	Histology	Stage		
1.	54	Endometrioid	Ia/G1	Endometrioid	Ia	78	Alive
2.	41	Endometrioid	Ib/G1	Mucinous	IIIc	79	Alive
3.	53	Endometrioid	Ib/G1	Mucinous	Ic	80	Death*
4.	51	Endometrioid	Ib/G1	Serous	Ia	178	Alive
5.	63	Endometrioid	Ia/G3	Endometrioid	Ia	168	Alive
6.	60	Endometrioid	Ib/G2	Clear cell	IIIc	36	Death*
7.	27	Endometrioid	Ib/G2	Serous	IIIb	76	Death*
8.	49	Endometrioid	Ib/G1	Serous	IIIa	137	Alive
9.	61	Endometrioid	Ia/G1	Serous	IIb	44	Death**
10.	63	Endometrioid	Ia/G1	Serous	IIIc	13	Death**
11.	41	Endometrioid	Ib/G2	Clear cell	IIc	15	Alive
12.	56	Endometrioid	Ib/G2	Serous	IIIc	14	Alive
13.	49	Endometrioid	Ia/G1	Clear cell	Ic	70	Alive
14.	47	Endometrioid	Ia/G1	Endometrioid	Ia	78	Alive
15.	40	Endometrioid	Ia/G2	Mucinou	IIIc	75	Alive
16.	44	Endometrioid	Ia/G2	Endometrioid	Ia	69	Alive
17.	63	Endometrioid	Ib/G2	Serous	Ic	46	Death*
18.	50	Mucinous + squamous	Ib/G2	Endometrioid	Ia	33	Alive
19.	52	Mucinous	Ib/G2	Endometrioid	IIIc	14	Alive
20.	62	Clear cell	Ib/G3	Clear cell	Ia	83	Alive

***** the cause of death is recurrence of the disease; ****** the cause of death is non-gynecologic malignancy

When only the patients with primary endometrial and ovarian cancer together were analyzed (n=20); OS was 81 months and DFS was 72 months. 5-year survival rate was 68% and 5-year DFS rate was 67%. Overall survival rates for patients with synchronous primary endometrial and ovarian cancer are also shown in Figure 1. Fifteen of these 20 patients received the same "taxol + platin" adjuvant chemotherapy (75%). Of these 15 patients, 12 (80%) were sensitive to platin chemotherapy whereas the other 3 (20%) were not. In platin sensitive patients, OS was 86 months and DFS was 81 months. In platin resistant patients, OS was 34 months and DFS was 29 months. Both OS and DFS were significantly higher in platin sensitive patients with p=0,028 and p=0,016, respectively.

There were 7 recurrences. 5 of them occurred in the ovarian -endometrial cancer group. 2 of 5 recurrences were recognized on the vaginal cuff, 2 were in the abdomen and the last was in the pelvis. The other 2 recurrences occurred in the cervical cancer patients. Both of them were recognized on the vaginal cuff.

Nine patients died during the follow up period. 6 of 7 patients with recurrence died due to the relapses. The other 3 patients died due to different non-gynecological malignancies, two breast cancers and one gastric cancer.

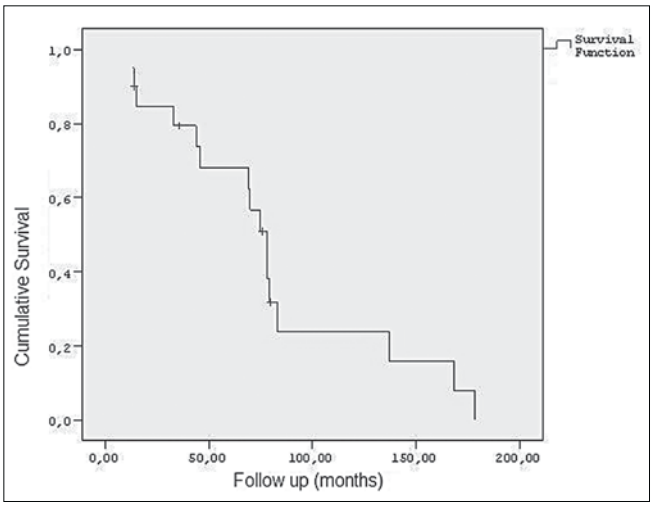

Figure 1. Overall survival for patients with synchronous primary endometrial and ovarian cancer patients. Data analysis was performed using Kaplan-Meier methods.

Discussion

Tumors of the female genital system are relatively common and may involve ovarian, endometrial, tubal, cervical, vaginal and vulvar cancers. Coexistence of more than one cancer at the same time is uncommon and seen in 1-6% of all gynecologic malignancies [1-3]. The most common togetherness in these tumors is the coexistence of endometrial and ovarian cancer. Ayhan et al. determined endometrial– ovarian tumors in 51.7% of women with synchronous primary gynecologic malignancies and Gungor et al found a similar ratio, 52.4% [3, 13]. In the present study 80% of synchronous primary gynecologic malignancies consisted of endometrial– ovarian tumors. The most important issue in these tumors is to differentiate them from the distant metastasis from the ovary to the endometrium or vice versa. This difference is not the issue for tumors with dissimilar histology in different organs. However, if the histological subtypes of the tumors are similar, the pathologist must differentiate metastasis from synchronous malignancy. In the present study, pathological criteria mentioned before were used to distinguish independent primary tumors from metastasis. Several molecular analysis methods were described to differentiate metastasis from synchronous malignancy such as DNA flow cytometry [14], loss of heterozygosity on chromosome [15], X-chromosome inactivation [16], PTEN/MMAC1 [17, 18], beta-catenin [19] and microsatellite instability [20]. However there is no consensus on which method is the most appropriate. In our study, there were five patients with similar histological subtypes in different organs. Four of them had endometrioid adenocarcinoma of the uterus and ovary, and one of them had clear cell carcinoma of the uterus and ovary. In these patients, both tumors were confined to the primary sites. Thus, they were accepted as synchronous tumors.

Average age in patients with synchronous genital malignancies is nearly 10-20 years earlier than those with single primary malignancies of the ovary or endometrium. Soliman et al. found a median age of 50 years at diagnosis in their review of 84 women with synchronous endometrial and ovarian tumors [21].

Chiang et al. found the mean age at diagnosis as 47.2 years, Tong et al found it as 45,2 years [22, 23]. In the present study the mean age at diagnosis was 53,6 years and comparable with the other results.

Nulliparity is a known risk factor for both endometrial and ovarian cancer. However, this topic is controversial in synchronous malignancies. Soliman et al. confirmed the role of nulliparity in developing synchronous endometrial and ovarian tumors [21]. Another study found that 50% of the women with synchronous endometrial–ovarian tumors were nulliparous [11]. But in another study, only one woman in 21 patients with synchronous endometrial and ovarian tumors was nulliparous [13]. In the present study, 2 of 25 patients were nulliparous. More comprehensive studies with larger sample sizes are necessary to elucidate this controversy.

Endometrial cancer can be detected at early stages with the most common presenting symptom of abnormal uterine bleeding, whereas ovarian cancer has vague symptoms such as abdominal distention or pelvic pain, and the latter can typically be detected at late stages. Soliman et al. found that 46% of patients had presented with abnormal uterine bleeding and 17% with abdominal or pelvic pain [21]. Gungor et al. reported that 44.4% of women with synchronous tumors suffered pelvic or abdominal pain at diagnosis and 33.3% had abnormal uterine bleeding [13]. In the present study, the most common presenting symptom was abnormal uterine bleeding with the incidence of 48%. These early symptoms may help early diagnosis of synchronous tumors and may improve the outcome for these patients. Especially in young patients with menometrorrhagia and asymptomatic adnexal mass, endometrial biopsy should be performed before the operation in order to rule out concomitant endometrial cancer.

It was reported that patients suffering from synchronous primary cancer were more favorable than patients showing metastatic lesions of individual tumors [1, 3, 11]. Zaino et al. reported that the estimated probability of surviving all causes of death for 5 years or more is 85.9% and that of surviving 10 years or more is 80.3% [4]. Tong et al. found that the mean survival of eight patients with synchronous endometrial and ovarian cancer was

54 months. The overall survival rate at 2 years was 70% [23]. Gungor et al. concluded that women with endometrial–ovarian tumors had a 5-year survival rate of 77%, suggesting a more favorable prognosis [13]. Soliman et al. and Chiang et al. grouped the patients as similar / dissimilar histology. According to Soliman et al. patients with synchronous endometrioid tumors of the endometrium and ovary (endometrioid/endometrioid) had a better median overall survival (119 months) than those with non-endometrioid or mixed histological subtypes (48 months) [21]. Chiang et al. reported that the mean survival in the group of similar histology (n=15) was 63 months, and 48 months in the group of dissimilar histology (n=12) [22].

In the present study, overall survival (OS) for all patients (n=25) was 87 months. OS was 81 months and DFS was 72 months for patients with endometrial-ovarian cancer (n=20). 5-year survival rate was 68% and 5-year DFS rate was 67% in these patients. These results are comparable with the results of the previous studies and more favorable than the outcome of metastatic primary gynecological tumors. We also divided the patients who had been given chemotherapy (n=15) as platin resistant (n=3) or platin sensitive (n=12). OS was 86 months and DFS was 81 months in platin sensitive patients. In platin resistant patients, OS was 34 months and DFS was 29 months. Both OS and DFS were significantly higher in platin sensitive patients.

Conclusion

In conclusion, synchronous gynecological malignancies are a rare clinical entity and develop at a younger age with a more favorable diagnosis. The most common presenting symptom is abnormal uterine bleeding. The clinician should always be suspicious about a synchronous malignancy with a malignant endometrial biopsy result at a younger age with an adnexal mass. Larger studies in the future will further elucidate the pathophysiology and the outcome of synchronous tumors of the female reproductive tract.

Authors' Contribution

1. Bahadır Saatli – concept, analysis and interpretation of data, revised article critically.
2. Nuri Yildirim –article draft, corresponding author, interpretation of data, concept, assumptions, study design.
3. Ali Cenk Ozay – acquisition of data, analysis and interpretation of data.
4. Meral Koyuncuoglu - acquisition of data, analysis and interpretation of data.
5. Binnaz Demirkan – assumptions, study design, acquisition of data.
6. Uğur Saygılı - revised article critically, concept.

Authors' statement

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