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 Eylül 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 /
Synchroniczne raka:

**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 Elyuł” 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 wynosiło 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 przerzędy.

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

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian + endometrial</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Ovarian + cervical</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Ovarian + endometrial + cervical</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Endometrial + tubal</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Endometrial + vulvar</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Endometrial cancer</th>
<th>Ovarian cancer</th>
<th>Survival (months)</th>
<th>Last Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Histology Stage/Grade</td>
<td>Histology Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>54</td>
<td>Endometrioid la/G1</td>
<td>Endometrioid la</td>
<td>78</td>
<td>Alive</td>
</tr>
<tr>
<td>2.</td>
<td>41</td>
<td>Endometrioid lb/G1</td>
<td>Mucinous llc</td>
<td>79</td>
<td>Alive</td>
</tr>
<tr>
<td>3.</td>
<td>53</td>
<td>Endometrioid lb/G1</td>
<td>Mucinous lc</td>
<td>80</td>
<td>Death*</td>
</tr>
<tr>
<td>4.</td>
<td>51</td>
<td>Endometrioid lb/G1</td>
<td>Serous la</td>
<td>178</td>
<td>Alive</td>
</tr>
<tr>
<td>5.</td>
<td>63</td>
<td>Endometrioid la/G3</td>
<td>Endometrioid la</td>
<td>168</td>
<td>Alive</td>
</tr>
<tr>
<td>6.</td>
<td>60</td>
<td>Endometrioid lb/G2</td>
<td>Clear cell llc</td>
<td>36</td>
<td>Death*</td>
</tr>
<tr>
<td>7.</td>
<td>27</td>
<td>Endometrioid lb/G2</td>
<td>Serous llb</td>
<td>76</td>
<td>Death*</td>
</tr>
<tr>
<td>8.</td>
<td>49</td>
<td>Endometrioid lb/G1</td>
<td>Serous Illa</td>
<td>137</td>
<td>Alive</td>
</tr>
<tr>
<td>9.</td>
<td>61</td>
<td>Endometrioid la/G1</td>
<td>Serous llb</td>
<td>44</td>
<td>Death**</td>
</tr>
<tr>
<td>10.</td>
<td>63</td>
<td>Endometrioid la/G1</td>
<td>Serous llc</td>
<td>13</td>
<td>Death**</td>
</tr>
<tr>
<td>11.</td>
<td>41</td>
<td>Endometrioid lb/G2</td>
<td>Clear cell llc</td>
<td>15</td>
<td>Alive</td>
</tr>
<tr>
<td>12.</td>
<td>56</td>
<td>Endometrioid lb/G2</td>
<td>Serous llc</td>
<td>14</td>
<td>Alive</td>
</tr>
<tr>
<td>13.</td>
<td>49</td>
<td>Endometrioid la/G1</td>
<td>Clear cell lc</td>
<td>70</td>
<td>Alive</td>
</tr>
<tr>
<td>14.</td>
<td>47</td>
<td>Endometrioid la/G1</td>
<td>Endometrioid la</td>
<td>78</td>
<td>Alive</td>
</tr>
<tr>
<td>15.</td>
<td>40</td>
<td>Endometrioid la/G2</td>
<td>Mucinous llc</td>
<td>75</td>
<td>Alive</td>
</tr>
<tr>
<td>16.</td>
<td>44</td>
<td>Endometrioid la/G2</td>
<td>Endometrioid la</td>
<td>69</td>
<td>Alive</td>
</tr>
<tr>
<td>17.</td>
<td>63</td>
<td>Endometrioid lb/G2</td>
<td>Serous lc</td>
<td>46</td>
<td>Death*</td>
</tr>
<tr>
<td>18.</td>
<td>50</td>
<td>Mucinous + squamous</td>
<td>Endometrioid la</td>
<td>33</td>
<td>Alive</td>
</tr>
<tr>
<td>19.</td>
<td>52</td>
<td>Mucinous lb/G2</td>
<td>Endometrioid llc</td>
<td>14</td>
<td>Alive</td>
</tr>
<tr>
<td>20.</td>
<td>62</td>
<td>Clear cell lb/G3</td>
<td>Clear cell la</td>
<td>83</td>
<td>Alive</td>
</tr>
</tbody>
</table>

* 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.

**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 endome trioid 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. Bahadir Saatli – concept, analysis and interpretation of data, revised article critically.
2. Nuri Yıldırım – article draft, corresponding author, interpretation of data, concept, assumptions, study design.
4. Meral Koyuncuoğlu - acquisition of data, analysis and interpretation of data.
5. Birnav Demirkan – assumptions, study design, acquisition of data.
6. Üğur Saygılı - revised article critically, concept.

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References