METASTATIC TUMORS OF THE OVARY: THE RATE OF INCIDENCE AND THE MOST FREQUENT SITES OF PRIMARY TUMORS

Zorica Stanojević¹, Biljana Djordjevic² and Olivera Dunjic³

Ovary is one of the main endocrine glands, also the source of female fertility and at the same time the organ with the largest number of histological varieties of malignant tumors. The most frequent among primary neoplasms are epithelial tumors. Secondary tumors of the ovary arise by direct tumor extension from adjacent organs or tissues, by transtubal or transperitoneal route, as well as hematogenously, limphogenously and by jatrogenic dissemination.

The aim of the study was to determine the frequency of metastatic ovarian tumors and to determine the most common sites of primary tumors.

The study group consisted of 488 patients with histopathologically confirmed malignant ovarian tumors treated at the Clinic of Oncology, Clinical Center Niš, in the period from January 1, 1998 to December 31, 2005. In order to determine the origin of metastatic tumors, beside histological and clinical examination, radiological, endoscopic and radioisotopic methods used.

Epithelial malignant tumors were found in 398/488 (81,56%) patients, sex cord tumors in 29/488 (5,94%) cases, germ cell tumors in 14/488 (2,87%) patients and mesenchimal tumors not specific for ovary in 6/488 (1,23%) cases. Metastatic ovarian tumors were verified in 41/488 (8,40%) patients. The most frequent ovarian secondary deposits derived from endometrial carcinoma (30/41, or 73,17%). Eight patients (19,51%) had breast carcinoma, 2/41 (4,88%) stomach carcinoma and 1/41 (2,44%) colorectal carcinoma. Average age of patients with metastatic ovarian tumors was significantly higher (p<0,05) compared with patients with primary ovarian tumors.

Metastatic tumors are an important group of ovarian neoplasms (8,40%). Metastases of endometrial and colorectal carcinoma are diagnosed during histopathological analysis of the primary tumor. All breast carcinomas are diagnosed before their ovarian secondary deposits, while in both cases of stomach carcinomas diagnosis of primary tumor was confirmed later. Acta Medica Medianae 2007;46(4):5-9.

Key words: ovary, secondary tumors, endometrium, breast, stomach, colorectal

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Introduction

Ovary is an organ of the female genital system most commonly invaded by metastases. Around 5-10% of all adnexal masses detected on physical examination are metastatic tumours of the ovary (MTO), though incidence rates for secondary tumors in this organ rise as high as 40%, depending on the geographical location of the performed study (1). Average age at diagnosis of MTO patients is lower compared to primary epithelial ovarian tumor (2). The finding can be attributed to ample blood supply to the ovary in premenopausal women and to the fact that prevalence of breast and stomach cancers (commonly metastasizing to the ovary) is highest around menopause (3).

Metastatic tumors can be confused with primary tumors of the ovary (4,5). The reasons for that should be sought in the fact that the tumors histopathologically similar to primary ovarian tumors most commonly give metastases to the ovary. By the incidence of secondary deposits, we may point out cancers of the colon, stomach, breast and endometrium, as well as lymphomas and leukemias (3,6-8). Ovarian metastases have been detected in 32-38% of breast cancer patients; 28-35% of women with colorectal cancer; and 16% of women with genital tract tumors (endometrium, uterine cervix, vagina, vulva) (9). Lately, special attention has been paid to mucinous tumours of the appendix, pancreas and biliary tract, which commonly spread to the ovary, resembling thus mucinous borderline tumor or mucinous ovarian carcinoma (10). Other malignant epithelial tumors, but also sarcomas and blastomas, can too metastasize to the ovary, though such metastases are fairly rare (11-27).
There are differences in the pattern of metastasizing of primary tumors to the ovary. Direct spread from the adjacent organs occurs in Fallopian tube carcinomas, corpus uteri cancer, and colorectal cancer; transtubal spread in endometrial cancer; and transperitoneal spread in tumors of the abdominal organs, such as appendix, stomach, pancreatic and biliary system tumors (8,28). Hematogenous and lympho-hous dissemination is also possible, as well as iatrogenic spread during laparoscopy or laparotomy (8,28,29).

Ovarian metastases can be detected during control examinations performed as tertiary prevention in patients previously treated for breast, stomach and colorectal cancer, but also during explorative laparotomy performed on account of the present adnexal mass. In only 1.5% of the cases breast cancer is detected after the diagnosis of its ovarian metastases, while in patients with gastrointestinal cancer ovarian metastases are usually identified during surgical treatment of the primary tumor (5,30). In 35% of the Krukenberg tumor cases, primary digestive tract diagnosis precedes the diagnosis of this tumor in the ovary (31). MTO symptomatology is unspecific. Most common symptoms are enlargement of the abdomen, sensations of weight and tension due to ascites, dysuric complaints, obstruction, and vaginal bleeding.

MTO are bilateral in 70% of the cases and present as multiple superficial or parenchymatous, mostly solid nodules of various sizes. Ovaries themselves can be slightly enlarged, but also sized more than 10 cm in diameter. The presence of implants on the surface of ovaries, multinodularity and intravascular tumor emboli are of use in the diagnosis of MTO which reached ovaries via abdominal cavity or Fallopian tubes (8).

Histopathologic appearance of most MTO is similar to the one in ovarian cancers. Differential diagnosis of primary and secondary malignant tumors of the ovary is difficult if it is based only on clinical and histopathologic characteristics of the tumor. Immunohistochemistry has an important role in differential diagnosis of primary and metastatic ovarian tumors, and thus in appropriate treatment administration and assessment of prognosis (8).

The presence of ovarian metastases is a sign of poor prognosis of the non-genital primary tumor. Surgical management is necessary both for diagnostic and for palliative purposes. Cytoreductive surgery is applied in a number of patients, aiming to prolong survival and to improve quality of life.

This paper aims at assessing the incidence of MTO and tries to establish the most common site of primary malignant tumor.

Material and methods

We enrolled in our study 488 patients with histopathologically confirmed malignant tumor of the ovary treated at the Clinic of Oncology, Clinical Centre Niš, in the period 1998-2005. All subjects were previously surgically treated, with either radical approach according to the protocol for surgical treatment of ovarian carcinoma, or with reductive surgery in cases of bulky disease. In 81 (16,60%) of patients only diagnostic and staging surgery was performed. Indications for surgical management were palpable masses in the pelvis and/or abdomen, positive echosono-graphy, presence of free liquid in the stomach, positive cytology and increased serum values of CA-125.

In our morphologic analysis we used biopsy samples or the samples of surgically removed organs. They were fixed in 10% neutral formalin, processed in the machine for automated tissue processing and embedded in paraffin. Preparations 5 µm thick were stained with hematoxylin and eosin (HE).

In order to establish the origin of metastatic tumor, in addition to histopathologic and clinical examination, we utilized radiologic, endoscopic and radioisotope techniques, and computerized tomography and nuclear magnetic resonance too as necessary. In the diagnosis of ovarian metastases of endometrial cancer the size of the tumor in both organs had a key role, in addition to histopathology of the tumor and intraoperative finding, on the basis of which pathologist and surgeon together decided on the nature of the primary tumor.

The results were presented as an arhythmic mean, standard deviation, variation interval (minimum-maximum) and structure index (%). We used Student’s t-test to establish the significance of differences we found. The differences were considered significant for the value of p<0.05.

Results

Table 1 presents the distribution of malignant ovarian tumors. Out of 488 patients with malignant ovarian tumors, 398 (81,56%) had epithelial malignancies, 29 (5,94%) had tumors of sex cord and stromal origin, 14 (2,87%) had germ-cell tumors, and 6 (1,23%) had ovary unspecific mesenchymal malignancies. MTO was histopathologically verified in 41 (8,40%) patients.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Epithelial tumors</td>
<td>398</td>
<td>81,56</td>
</tr>
<tr>
<td>Sex cord and tumors of stromal origin</td>
<td>29</td>
<td>5,94</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>14</td>
<td>2,87</td>
</tr>
<tr>
<td>Mesenchymal tumors non-specific for the ovary</td>
<td>6</td>
<td>1,23</td>
</tr>
<tr>
<td>Metastatic tumors</td>
<td>41</td>
<td>8,40</td>
</tr>
<tr>
<td>TOTAL</td>
<td>488</td>
<td>100,00</td>
</tr>
</tbody>
</table>

Average age of patients with primary ovarian cancer was 54.50±12.5 years (range, 16-79 years), while those with metastatic cancer were somewhat older – 59,17±8,97 (range, 37-75 years). The difference was statistically significant (t-test, p<0,05).
Ovarian metastases are disease stage, tumor size, differential diagnosis of primary and metastatic neoplasms, and histopathologic criteria used in the diagnosis of primary and metastatic ovarian tumors. Ovarian metastases of endometrial and colon carcinoma most commonly metastasized to the ovary (30/41, or 73,17%) and it was usually endometrioid type disease histopathologically confirmed in 25 (60,97%) cases. In the remaining 5 cases, ovarian metastases of clear cell endometrial cancer were found in 3 (7,32%) women, and ovarian metastases of serous endometrial cancer were found in 2 (4,88%) cases. All endometrioid-type endometrial cancers were FIGO IIIA disease at the moment of surgery, in contrast to clear cell and serous carcinomas, which were FIGO IIIB or IIIC disease at the time of explorative laparotomy.

Out of 11 (26,83%) extragenital carcinomas with ovarian metastases, 8/41 (19,51%) had breast cancer, 2/41 (4,88%) had stomach cancer, while 1/41 (2,44%) had colon cancer (Table 2).

The overall incidence of bilateral metastatic tumors was 70,73%. All ovarian metastases of extragenital cancers were bilateral, while in endometrial cancer bilateral ovarian metastases were identified in 18 (59,99%) patients.

Ovarian metastases of endometriod and carcinoma of the colon were diagnosed during histopathologic analysis of the primary tumor. All breast cancers were identified before secondary ovarian deposits become evident, while in both cases of stomach carcinoma primary tumor was diagnosed only after the secondary ovarian deposits were confirmed.

**Discussion**

Metastatic tumors of the ovary comprise a significant group of ovarian neoplasms, not only because of their incidence rate, but also because of diagnostic difficulties occurring when tumors histopathologically similar to primary ovarian neoplasms give metastases to the ovary (1, 8). Clinical and histopathologic criteria used in differential diagnosis of primary and metastatic ovarian cancers are disease stage, tumor size, histologic grade and type, presence of angioinvasion, bilaterality and multinodularity of tumors, as well as initial clinical symptoms (8). The information on previously treated or still existing primary tumor in some other organ is extremely important in histopathologic evaluation of malignant ovarian tumors (32). If histopathologic findings indicate MTO, additional diagnostic procedures are mandatory in order to identify the primary tumor. Liver or lung metastases, without extensive peritoneal dissemination, are not common in primary ovarian malignancies.

There are numerous reasons accounting for the fact that real incidence of MTO is very hard to establish. One of them is that the incidence of MTO has been established based on autopsy findings, and in other studies based on intraoperative and biopsy findings (33). There are geographic variations in incidence of secondary ovarian tumors which can be explained by variable prevalence of certain primary malignancies. In a study in Japan, metastatic ovarian cancer was identified in as high as 40% of all ovarian neoplasms, which can be explained by the fact that stomach cancer, commonly metastasizing to the ovary, has the highest prevalence in this country (34). Finally, on exploration during surgery for colorectal cancer and other abdominal malignancies as well a macroscopically intact ovary may contain microscopically visible secondary deposits. In our series, secondary ovarian tumors were confirmed in 8.40% of cases, which is in accordance with literature data that MTO make up for 5-10% of all ovarian neoplasms (1, 35-37).

According to the available data, MTO patients are younger than those with malignant ovarian tumor of epithelial origin, which can be attributed to the fact that the prevalence of breast and stomach cancers, commonly metastasizing to the ovary, is highest around the time of menopause (2,3). In this investigation MTO patients were older than those with primary ovarian cancer (the difference was statistically significant), the fact that should be expected since in majority (73.17%) of patients ovarian metastases originated from endometrial carcinoma. Endometrial carcinoma most commonly occur in postmenopause, with incidence peaking around the age of 62 (8).

Carcinomas of the endometrium, breast, colon and stomach most commonly give metastases to the ovary, but neoplasms of the hematopoietic tissue should also be mentioned (3, 8). Endometrial carcinoma is the most common tumor of the genital organs that gives metastases to the ovary, while ovarian metastases of the Fallopian tube, uterine cervix, vaginal and vulvar cancers, are extremely rare (3). In the investigated series, secondary ovarian malignancies were most commonly identified in endometrial cancer (73,17%); there were no ovarian metastases of other genital malignancies. Out of all extragenital tumors giving ovarian metastases, most patients (19,51%) had breast cancer, 4.88% stomach cancer, while 2,44% had colon cancer, which agrees with the literature data (3).

Ovarian metastases are bilateral in around 70% of the cases (9). Total incidence of bilateral MTO in our study was 70,73%. All non-genital ovarian meta-

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**Table 2. Distribution of metastatic ovarian tumors based on their origin and histopathology of the primary lesion**

<table>
<thead>
<tr>
<th>Primary malignant tumor</th>
<th>Metastatic ovarian tumor</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Genital (total)</td>
<td></td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>30</td>
</tr>
<tr>
<td>Endometriod</td>
<td>25</td>
</tr>
<tr>
<td>Clear cell</td>
<td>3</td>
</tr>
<tr>
<td>Serous</td>
<td>2</td>
</tr>
<tr>
<td>Extragenital (total)</td>
<td>11</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>8</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>2</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1</td>
</tr>
</tbody>
</table>
Ovarian metastases of endometrial cancer and cancers of the gastrointestinal tract are commonly identified during surgical management and histopathologic analysis of the primary tumor. In 35% of Krukenberg tumor cases, diagnosis of the primary digestive tract tumor precedes the detection of ovarian metastases of that neoplasm (31). Breast cancer is detected after the diagnosis of ovarian metastases in just 1.5% of cases (5). In our study, ovarian metastases of endometrial and colorectal cancer were diagnosed during histopathologic analysis of the primary tumor. All breast cancers were diagnosed before secondary ovarian deposits were detected, while in both cases of stomach cancer, diagnosis of the primary tumor was made after the detection of ovarian metastases.

**Conclusion**

Metastatic tumors are an important group of ovarian neoplasms (8.40%), occurring in younger patients compared to primary ovarian malignancies. Metastases of endometrial and colon carcinoma were diagnosed during histopathologic analysis of primary tumor. All breast cancers were diagnosed before ovarian metastases, while in both stomach cancer cases diagnosis of the primary tumor was made after the detection of ovarian metastases.

**Literatura**

Jajnik je jedna od glavnih endokrinih žlezda, izvor je fertilnosti žene i u isto vreme i simptomi terminacije žene. Metastatski tumori jajnika (MTJ) posledica su direktnog širenja tumora sa susednih organa, transtubarnog ili transperitonealnog širenja, kao i hematogene, limfogene i jatrogene diseminacije. Cilj rada je da se ispita učestalost MTJ i utvrdi najčešća lokalizacija primarnog malignog tumora.


Epitelni maligni tumor imalo je 398 (81,56%) bolesnica, tumor porekla polnih traka i strome 29 (5,94%), tumor porekla germinativnih čelija 14 (2,87%) bolesnica i mezenhimi tumor koji nije specifičan za ovarijum 6 (1,23%). Kod 41 (8,40%) bolesnice verifikovan je MTJ. U jajnik je najčešće metastazirao karcinom endometrijuma (30,41, ili 73,17%). Osam bolesnica (19,51%) imalo je karcinom dojke, 2/41 (4,88%) karcinom želuca i 1/41 (2,44%) kolorektalni karcinom. Prosječna starost bolesnica sa MTJ bila je signifikantno veća (p<0,05) u odnosu na bolesnice sa primarnim malignim epitelnim tumorom jajnika.