Characteristics and prognosis of ovarian metastatic tumors: review of a single-institution experience

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Summary

Background: To evaluate the clinico-pathological characteristics and role of surgery in patients with ovarian metastasis. *Materials and Methods:* Clinical data from 51 patients with pathologically confirmed ovarian metastasis were reviewed. *Results:* Ovarian metastasis accounted for 14% of all malignant ovarian neoplasms (51/364). Of the 51 metastatic ovarian tumor cases, 24 originated from gynecologic malignancies, while 27 originated from non-gynecologic malignancies. Optimal cytoreduction was performed in 88% and 37% of patients with metastases of gynecologic and non-gynecologic origin, respectively. Patients with ovarian metastasis had a two-year survival rate in 82% of the gynecologic group and 70% of the non-gynecologic group ($p = 0.35$). The five-year survival rate of patients with non-gynecologic tumor origin (29%) was significantly worse ($p = 0.04$) than the survival rates of those with tumors of gynecologic origin (61%). In the non-gynecologic group, the five-year survival rates were significantly different between patients who were performed optimal cytoreductive surgery vs those without this procedure (42% and 20%, respectively; $p = 0.04$). *Conclusion:* Although complete surgical resection is not achievable in approximately two-thirds of patients with metastases of non-gynecological origin, optimal tumor cytoreduction appears to improve survival, which is statistically significant in all patients with ovarian metastatic tumors.

Key words: Ovarian metastasis; Cytoreductive surgery; Krukenberg tumor.

Introduction

The ovaries are frequent sites of metastasis for malignancies originating from gynecologic and non-gynecologic areas. Metastatic ovarian tumors account for 5%-30% of all malignant ovarian tumors [1]. This frequency seems to be associated with the prevalence and spreading patterns of primary malignancy. The majority of non-gynecologic cancer metastasis to the ovaries originates from the gastrointestinal (GI) tract and breasts [2]. Another frequent primary site is the gynecologic tract. In many cases, it can be difficult to distinguish between primary and metastatic ovarian tumors. Some authors reported that 45% of metastatic ovarian tumors originating from colon cancer were misdiagnosed as primary ovarian cancer due to the mucin-producing pattern of these tumors [2, 3]. Additionally, ovarian metastasis is commonly detected before primary tumor [4]. Distinguishing between primary and metastatic ovarian tumors is important because misinterpretation may lead to inappropriate management and suboptimal treatment outcomes.

According to previous studies, tumors of non-gynecologic origin with ovarian metastasis have worse prognosis than tumors of gynecologic origin with ovarian metastasis and primary ovarian cancer [5, 6]. Although cytoreductive surgery and adjuvant chemotherapy have a proven role in primary epithelial ovarian cancer, there is limited information regarding the benefits of cytoreductive surgery in patients with metastatic ovarian tumors of gynecologic and non-gynecologic origin. The purpose of this study was to assess the clinical characteristics, to evaluate the role of surgery, and to compare the survival rates in 51 cases of metastatic ovarian tumors of gynecologic and non-gynecologic origin.

Materials and Methods

The Institutional review board approved this study. A total of 51 patients with ovarian metastasis from gynecologic and non-gynecologic primary sites were identified at the Bakirkoy Woman and Children Training and Research Hospital between 2002 and 2010. During this time, 313 cases of primary malignant ovarian tumors were resected and histopathologically diagnosed. The available clinical records of patients with ovarian metastasis were reviewed for age, menopausal status, clinical manifestation of metastasis, serum CA-125 levels, intraoperative findings, primary site of origin, adjuvant treatment, and the effect of surgery on survival. The distinction between primary and metastatic tumors was based on the diagnostic approach of Young and Scully [7]. The diagnosis of ovarian metastasis was confirmed by histological and immunohistochemical stains (cytokeratin 7 and 20) in selected cases. The categorized surgical modalities are as follows: (1) total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH+BSO), omentectomy, and bilateral pelvic and para-aortic lymphadenectomy (PPALND) with complete cytoreduction; (2) TAH+BSO and omentectomy with incomplete removal of the primary tumor; and (3) minimal surgical effort including salpingo-oophorectomy, wedge resection, or biopsy of ovarian masses. Cytoreductive surgery was defined as optimal when the largest residual tumor mass was less than one cm.

Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Pearson's chi-square or Fisher's exact test was used to analyze the categorical variables. Survival analyses were estimated by the Kaplan-Meier method, and dif-

ferences between groups were calculated using the log-rank test. All intervals were determined from the date of surgery. The results were considered statistically significant if the *p* value was < 0.05.

Results

During the nine-year study period, 51 cases of ovarian metastases and 313 cases of primary ovarian malignancies, including synchronous primary ovarian tumors, were identified at the Institutions. According to these data, ovarian metastases comprise 14% (51/364) of all malignant ovarian neoplasms. The mean age of the study group was 50.8 ± 12.2 years (range 29 - 72). Of the 51 metastatic ovarian tumor cases, 24 (47%) originated from gynecologic malignancies while 27 (53%) originated from non-gynecologic malignancies. Metastatic non-gynecologic tumors occurred in a slightly younger age group than metastatic gynecologic tumors (49.3 vs 52.5). Postmenopausal patients accounted for 41% and 46% of the non-gynecologic and gynecologic groups, respectively. The most common presenting symptoms of tumors of non-gynecologic origin were increased abdominal girth (63%) and abdominal/pelvic pain or discomfort (26%); however, abnormal uterine bleeding (58%) was the most commonly seen symptom in malignancies of gynecologic origin. Serum CA-125 was used as a tumor marker for most patients (84%) in this study. The median serum CA-125 level was 245 U/ml (range 14 - 1,352) and 348 U/ml (range 13 - 5,734) for metastatic ovarian tumors of gynecologic origin and non-gynecologic origin, respectively ($p = 0.19$).

In the gynecologic group, uterine corpus was the most common primary site (29.4%), followed by uterine cervix (9.8%), and Fallopian tube (7.8%). Fourteen cases of uterine corpus tumors were adenocarcinomas (six endometrioid, three serous, three clear cell, and two otherwise unspecified), while one case was endometrial stromal sarcoma. The histological types of uterine cervical cancers included two adenocarcinomas and three squamous cell carcinomas. Additionally, four cases of Fallopian tube malignancies with ovarian metastasis consisted of one Wolffian tumor and three cases of tubal adenocarcinoma. In the non-gynecologic group, anatomic locations of primary tumors were as follows: colon (25%), stomach (9.8%), breast (5.9%), and appendix (3.9%). There were also tumors of unknown primary origin (9.8%), but most had histopathological features resembling an upper GI tract or colon origin (Table 1). Mucin-producing adenocarcinomas were the most commonly identified histological type of non-gynecologic metastatic tumors (70%). However, a signet-ring cell component was found in six of all ovarian metastases (12%) and accounted for 19% and 4% of non-gynecologic and gynecologic metastatic ovarian tumors, respectively.

Bilateral ovarian involvement was present in 33% of the gynecologic group and 74% of the non-gynecologic group ($p = 0.01$). On the other hand, a minimum of uni-

Table 1. — *Primary sites of ovarian metastatic tumors.*

Site	No. of patient (%)
Non-gynecologic origin	27 (52.9)
Colorectal	12 (25)
Stomach	5 (9.8)
Breast	3 (5.9)
Appendix	2 (3.9)
Tumor of unknown origin	5 (9.8)
Gynecologic origin	24 (47.1)
Endometrium	14 (27.4)
Cervix	5 (9.8)
Fallopian tube	4 (7.8)
Sarcoma	1 (2)

Table 2. — *Clinico-pathologic characteristics of patients with metastatic ovarian tumors.*

	Non-gynecologic origin (n = 27)	Gynecologic origin (n = 24)	*p* value
Age (mean ± SD)	49.3 ± 12.6	52.5 ± 11.7	0.27
Postmenopausal	41%	46%	0.73
Symptom			
Abdominal distension	63%	29%	
Abdominal/pelvic pain	26%	8%	
Abnormal uterine bleeding	7%	58%	
Asymptomatic	7%	8%	
Ascites			
Positive	89%	46%	0.002
CA-125 (median)	348 U/ml	245 U/ml	0.19
Bilaterality	74%	33%	0.01
Occult metastases	4%	29%	0.02
Mean sizes of the largest masses	5.9 cm	7.1 cm	0.13
Surgery types			
Extensive surgery[*]	37%	88%	
TAH+BSO	52%	12%	
Minimal surgical effort[†]	11%		

[*] Total abdominal hysterectomy, bilateral salpingo-oopherectomy, omentectomy, pelvic and para-aortic lymphadenectomy, and complete debulking of the tumor.
[†] Salpingo-oopherectomy, wedge resection, or biopsy of ovarian masses.

lateral prominently-enlarged ovarian masses were observed in 71% of metastases of gynecologic origin and 96% of metastases of non-gynecologic origin, proving that occult metastasis was present in 29% of the gynecologic group and 4% of the non-gynecologic group. The sizes of the ovaries in the metastatic disease were recorded in 43 out of 51 patients. The mean sizes of the largest masses for the gynecologic and non-gynecologic groups were 5.9 cm (range 3 - 10) and 7.1 cm (range 3 - 12), respectively ($p = 0.13$). Demographics, clinical and pathological features, as well as the differences of the constituent ratio are compared between these two subgroups in Table 2.

Extensive surgical resection was performed in 88% of gynecologic origin metastatic tumors (21/24). In the non-gynecologic group, TAH + BSO, omentectomy, and PPALND with complete cytoreduction were performed in ten patients (37%); 14 patients (52%) had TAH + BSO + omentectomy with incomplete removal of the primary tumor; and three patients (11%) had minimal surgical effort, including salpingo-oophorectomy, wedge resec-
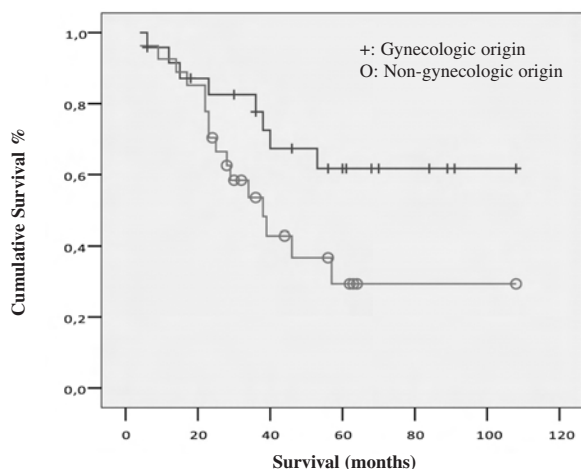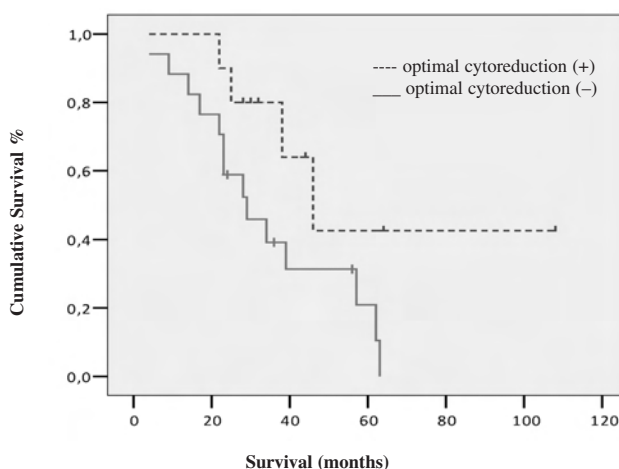
Fig. 1

Fig. 2

Figure 1. — Survival curves of patients with metastatic ovarian tumors according to primary origin.
Figure 2. — Survival curves of patients with non-gynecologic origin metastatic ovarian tumors according to cytoreductive surgery.

tion or biopsy of ovarian masses. Colon resection was performed in five out of 14 patients with appendix-colorectal cancer during initial cytoreductive surgery (36%). Of 27 patients, ten (37%) were optimally cytoreduced, and 17 (63%) had suboptimal residual disease. All patients received adjuvant therapy; 69% had chemotherapy alone, 10% had radiotherapy alone, and 21% had chemotherapy and radiotherapy combined after surgery.

Follow-up began with the surgery of metastatic ovarian tumors, and the mean follow-up for these tumors was 43 months. The overall two- and five-year survival rates of 51 patients was 77% and 53%, respectively. Patients with ovarian metastasis had a two-year survival rate of 82% in the gynecologic origin group and 70% in the non-gynecologic group; however, the difference in two-year survival rates was not statistically significant ($p = 0.35$). The five-year survival rate of patients with a tumor of non-gynecologic origin (29%) was significantly worse ($p = 0.04$) than patients with a tumor of gynecologic origin (61%). The median survival time for patients who underwent optimal cytoreductive surgery was significantly superior to those who had suboptimal cytoreductive surgery (46 vs 29 months) in the non-gynecologic group. The five-year survival rates were significantly different between patients with and without cytoreductive surgery in the non-gynecologic group (42% and 20%, respectively; $p = 0.04$). Survival rates of patients are shown in Figures 1 and 2.

Discussion

The most common primary cancers that metastasize to the ovaries in the Western series are: colon, followed by stomach, breast, and gynecologic cancers [8], whereas stomach cancer was common in Eastern Asia and especially in Japan [9]. In this current study, metastatic ovarian tumors accounted for 14% of all ovarian malignancies and the GI tract (colorectal-appendix 28.9%, stomach 9.8%) was the most common primary site. These findings are consistent with previous studies. Webb *et al*. reported the GI tract as the primary site in 47%, breast in 31%, and gynecologic organs in 18% of cases [8]. Ulbright *et al*. demonstrated a 7% incidence of ovarian metastasis in patients who were thought to have a primary ovarian malignancy and also reported gastric cancers contributed 8% of metastatic ovarian lesions, similar to 9.8% seen in this series [2].

The mean age was 50.8 years in this study. Metastatic tumors of non-gynecologic origin occurred in a slightly younger age group than those with metastatic tumors of gynecologic origin (49.3 vs 52.5, respectively, $p = 0.27$). Although both gynecologic and GI malignancies are seen in later decades of life, it is quite concerning that patients with ovarian metastasis are rather a younger population. In the authors' opinion, there might be a relation between higher blood flow to the ovaries in earlier decades of life and increased risk of metastasis.

Occasionally, metastatic ovarian tumors morphologically and clinically resemble a primary ovarian neoplasm [10]. Furthermore, the radiological features of metastatic ovarian cancer show considerable variability. In this series, although the majority of patients underwent additional radiological assessment (65%) and gastroscopic/colonoscopic examination (25%), primary tumors of non-gynecologic group were known prior to resection of ovarian metastasis in only 11% of cases. Ayhan *et al*. [5] reported that the clinical diagnosis of primary tumor preceded the metastatic ovarian lesion in only 30% of patients and were mostly in patients with breast cancer (86%).

The incidence of bilaterality in metastatic ovarian cancers ranged from 54% to 70% [2, 5, 11]. In this series, the bilaterality ratio was 33% and 74% for gynecologic and non-gynecologic origin tumors, respectively ($p = 0.01$). Although bilaterality is far more frequent in the non-gynecologic group, occult metastasis was only 4%. The

reason for rarity of occult metastases in patients with tumors of non-gynecologic origin is that many of these were in advanced stages. On the other hand, it was significantly higher in metastatic tumors of endometrial (29%, 4/14) and cervical (40%, 2/5) origin.

For metastatic tumors of gynecologic origin, uterine corpus was the most common primary site. The frequency of metastatic endometrial adenocarcinomas was double that of cervical and tubal metastatic cancers combined. During the nine-year period of data collection, there were 304 cases of endometrial adenocarcinomas and 144 cases of uterine cervical cancers (112 cases of squamous cell carcinoma, and 32 cases of adenocarcinoma). The rates of ovarian metastasis in endometrial adenocarcinoma and uterine cervical cancer were 4.6% and 3.4%, respectively.

Although metastatic ovarian tumors are frequently called Krukenberg tumors, in this study, the authors have used the original definition of Woodruff and Novac: "a tumor arising in the ovarian stroma having characteristic mucin-filled, signet-ring cells" [12]. Krukenberg tumors accounted for 12% (6/51) of metastatic ovarian tumors; the primary tumor was most frequently located in the stomach (5/6). Song *et al*. [13] and Cheong *et al*. [14] reported that the incidence of the stomach as primary site of a Krukenberg tumor were 70% and 94%, respectively, which is consistent with the results of this current study (83%).

Ovarian metastases from other primary sites are manifestations of advanced disease; thus, the prognosis is generally poor. Petru *el al*. reported that the overall actuarial five-year survival rate was 10% in patients with non-gynecologic metastatic tumor [4]. In this present series, the overall five-year survival rate of patients with metastatic ovarian tumors originating from gynecologic and non-gynecologic organs were significantly different (61% and 29%, respectively; *p* = 0.04). This poor survival rate is consistent with the Yada-Hashimoto's study [1] which reports that the five-year survival rate of patients with metastatic ovarian tumors originating from gynecologic and non-gynecologic organs were 47% and 19%, respectively.

The extent of disease, biologic aggressiveness of the tumor, and the presence of a complete surgical resection have significant roles in the survival of patients with primary ovarian tumors. Nevertheless there is limited information regarding the outcome of patients with ovarian metastatic tumors that undergo cytoreduction. Some reports compared the survival rates of complete surgical resection vs palliative approach, especially in patients with colorectal cancer with ovarian metastasis. In these reports, better survival rates were demonstrated in cases that underwent complete debulking [2, 15]. In contrast, Miller *et al*. suggested that tumor reduction should be avoided and a palliative approach should be taken [10]. In this present series, cytoreductive surgery seemed to be beneficial in all patients with ovarian metastatic tumors. The median survival time was significantly superior in patients who underwent optimal cytoreductive surgery compared to those who underwent suboptimal cytoreduc-

tive surgery (46 vs 29 months) in the non-gynecologic group. As well, the five-year survival rates were significantly different between patients with and without optimal cytoreductive surgery in the non-gynecologic group (42% and 20%, respectively; *p* = 0.04).

In conclusion, although complete surgical resection is not achievable in approximately two-thirds of patients with metastases of non-gynecological origin, optimal tumor cytoreduction appears to improve the survival rate, which is statistically significant in all patients with ovarian metastatic tumors. Nevertheless, patients with gynecologic tumor origin have significantly higher survival rates than patients with non-gynecologic tumor origin.

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