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Surgical management and outcomes of metastatic tumors to the ovaries

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Summary

Purpose of Investigation: Gynecologic and non-gynecologic tumors occasionally metastasize to the ovaries. Aim of this study was to describe the clinicopathologic characteristics and survival outcomes of patients with metastatic tumors to the ovaries. *Materials and Methods:* Between 2007-2017, 859 operations were performed in this center with initial diagnosis of ovarian mass. Seventy-five patients who had metastatic tumor to the ovaries in pathological examination were included the study. *Results:* Median overall survival of all patients was 26 ± 5.9 months, three-year survival was 62%, and five-year survival was 37%. Patients who developed metachronous metastasis had better survival than patients who had synchronous metastasis ($p = 0.05$). Bilateral ovarian involvement was related with poor survival compared with unilateral involvement. Chemotherapy had beneficial effect on overall survival. Median survival in extensive surgery group was 30.9 months and it was better than minimal surgery group with 15.6 months, however it was not statistically significant ($p = 0.973$). *Conclusion:* The prognosis of the metastatic tumors to the ovaries is poor but achieving a complete resection and optimal debulking surgery may improve survival in some histologic subgroups.

Key words: Ovarian metastasis; Krukenberg tumors; Non-genital cancers; Chemotherapy; Cytoreductive surgery.

İntroduction

The most common origin of secondary tumors of the ovary are breast, gastric, colorectal, endometrial, and appendiceal cancers [1]. While primary tumor is the main determinant of survival, metastatic tumors have worse prognosis than primary ovarian cancers (five-year survival rate of 18.5 *vs*. 40%) [2, 3]. Management of metastatic tumors to the ovaries is controversial for surgeons, but many retrospective studies showed that cytoreductive surgery is useful in some histologic groups. Colorectal cancer patients are the best candidates because the survival benefit of extensive surgery has been demonstrated in most studies and the evidence supporting metastasectomy in other subtypes are less clear [4-6]. Subsequent treatment approaches such as chemotherapy or radiotherapy also remains controversial. Aim of this study was to describe clinical outcomes of cytoreductive surgery in metastatic tumors to the ovaries and present the single center experience over a ten-year period.

Materials and Methods

Using computer database, all patients operated between January 2007 and July 2017 who were diagnosed with metastatic tumor to the ovaries in Baskent University Ankara Hospital were identified. Seventy-five patients were eligible for this study and all charts were reviewed in detail. Except for seven, 75 patients had extensive surgery. Surgical procedures were categorized under two groups: minimal surgery and extensive surgery. Extensive surgery was considered as total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO), and bilateral pelvic-para-aortic lymphadenectomy (BPPALND), optimal debulking surgery (residual tumor < 1 centimeter), and in the presence of synchronous metastasis completion of primary resection (PR). Minimal surgery was considered as only TAH+BSO. Clinical and pathological variables included age, menopausal status, primary site, metastasis form, surgical treatment modalities, ovarian involvement, lymph node status, and chemotherapy. Synchronous metastasis was defined as metastatic tumor detected at the time of primary surgery and metachronous after the surgery. Endometrial cancers metastasizing to the ovaries distinguished by pathologic evaluation from epithelial ovarian cancer can exist at the same time with endometrial cancers.

Using Kaplan-Meier curves, overall survival was calculated for each histologic subgroup and all population from the date of diagnosis of the primary tumor or ovarian metastasis to the date of death or last follow-up. The difference in survival rates was compared using the log-rank test. SPSS version 23 was used in all analyses. *P* value of less than 0.05 was considered statistically significant.

Results

Seventy-five patients who were diagnosed with metastatic cancer to the ovaries were included in the study. Clinical and pathologic characteristics of patients are pre-

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Table 1. — *Demographic characteristics of patients with metastatic cancer to the ovaries.*

		Gastric (n=13)	Colorectal (n=27)	Breast (n=5)	Appendix (n=10)	Peritoneal mesothelioma (n=5)	Pancreatic-biliary (n=2)	Duodenum (n=1)	Endometrium (n=12)
Age (years)		42.8±10.0	51.0±14.7	49.4±8.4	55.3±13.3	46.8±17.6	58.5±19.1	59.0±0.0	60.2±14.3
Menopausal status	Premenopausal	9 (69%)	12 (44%)	1 (20%)	5 (50%)	2 (40%)	-	-	3 (25%)
	Postmenopausal	4 (21%)	15 (56%)	4 (80%)	5 (50%)	3 (60%)	2 (100%)	1 (100%)	9 (75%)
Metastasis	Synchronous	11 (85%)	20 (74%)	-	9 (90%)	5 (100%)	2 (100%)	1 (100%)	12 (100%)
	Metachronous	2 (15%)	7 (26%)	5 (100%)	1 (10%)	-	-	-	-
Surgical procedure*	TAH + BSO + BPPLND + omentectomy + appendectomy + colon resection + RLND	-	19 (70%)	-	6 (60%)	-	-	-	-
	TAH + BSO + BPPLND + omentectomy + appendectomy + gastrectomy	2 (15%)	-	-	-	-	-	-	-
	TAH + BSO + BPPLND + omentectomy + appendectomy	8 (62%)	7 (26%)	4 (80%)	4 (40%)	5 (100%)	-	1 (100%)	12 (100%)
	TAH + BSO	3 (23%)	1 (4%)	1 (20%)	-	-	2 (100%)	-	-
Ovarian involvement	Right or left	2 (15%)	10 (37%)	-	1 (10%)	-	1 (50%)	-	5 (42%)
	Bilateral	11 (85%)	17 (63%)	5 (100%)	9 (90%)	5 (100%)	1 (50%)	1 (100%)	7 (58%)
Lymph node	Negative	5 (39%)	9 (33%)	1 (20%)	8 (80%)	3 (60%)	2 (100%)	1 (100%)	3 (25%)
	Positive	8 (61%)	18 (67%)	4 (80%)	2 (20%)	2 (40%)	-	-	9 (75%)
Omental involvement	Negative	2 (15%)	9 (33%)	2 (40%)	1 (10%)	-	-	-	5 (42%)
	Positive	11 (85%)	18 (67%)	3 (60%)	9 (90%)	5 (100%)	2 (100%)	1 (100%)	7 (58%)
Cytology	Negative	4 (31%)	13 (48%)	3 (60%)	2 (20%)	-	2 (100%)	1 (100%)	4 (33%)
	Positive	9 (69%)	14 (52%)	2 (40%)	8 (80%)	5 (100%)	-	-	8 (67%)
Chemotherapy	No	1 (8%)	3 (11%)	-	2 (20%)	1 (20%)	-	1 (100%)	2 (17%)
	Yes	12 (92%)	24 (89%)	5 (100%)	8 (80%)	4 (80%)	2 (100%)	-	10 (83%)
Survival (months)	After surgery	8.9	25.3	16.9	18.2	42.2	5.1	2.5	67.4
	After diagnosis	9.1	31	99.2	18.2	42.2	5.1	2.5	67.4

**Total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic-para-aortic lymphatic dissection.*

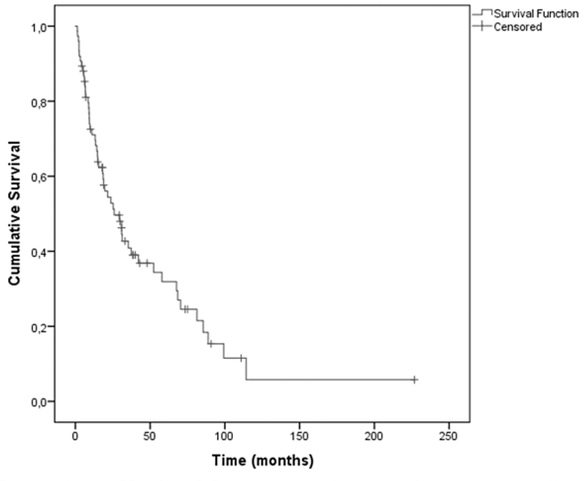

Figure 1. — Kaplan-Meier survival curve showing overall survival of all patients (n=75).

sented in Table 1. They were approximately 9% of all malignant ovarian tumors operated during the study period in this center (75/859). Median overall survival (Figure 1) was 26 ± 5.9 months three-year survival was 62%, and five-year survival was 37%. Sixty-eight (90.7%) patients underwent extensive surgery. Median survival in extensive surgery group was 30.9 months and it was better than minimal surgery group with 15.6 months, however it was not statistically significant ($p = 0.973$). Sixty (80%) patients had synchronous metastasis and initially treated by gynecologic oncologist, 15 (20%) patients had metachronous metastasis, and formerly had been treated by other surgeons with medical oncologists. Metachronous metastatic disease was surgically treated by gynecologic oncologists at the time of ovarian metastasis development. Metachronous metastatic patients live longer than synchronous metastatic patients (Figure 2) when survival is calculated from the time of disease diagnosis ($p = 0.05$). From the gynecologic operation,

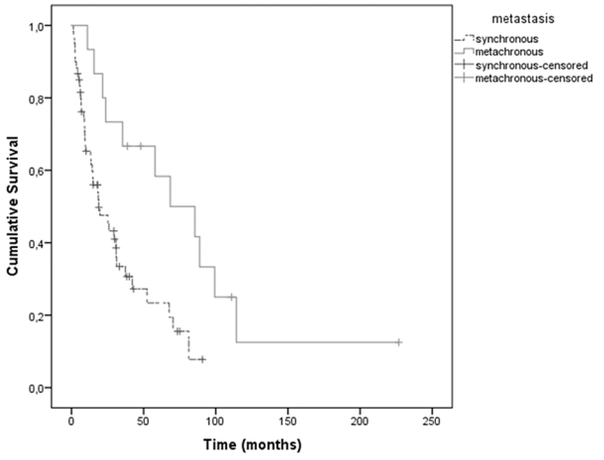

Figure 2. — Kaplan-Meier survival curves showing the effect of timing of metastasis on patients with ovarian metastasis ($p = 0.05$, log-rank test).

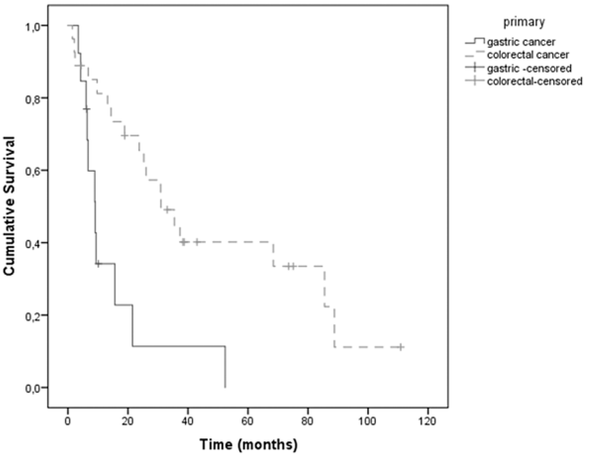

Figure 3. — Kaplan-Meier survival curves showing the effect of primary on patients with ovarian metastasis of gastric and colorectal origin ($p = 0.01$, log-rank test)

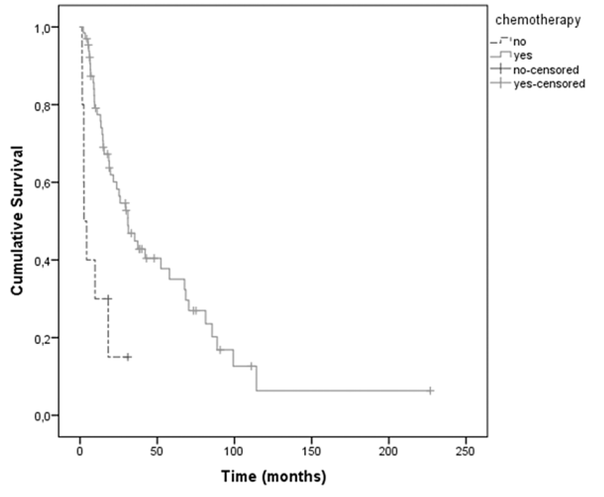

Figure 4. — Kaplan-Meier survival curves showing the effect of chemotherapy on patients with ovarian metastasis ($p = 0.003$, log-rank test).

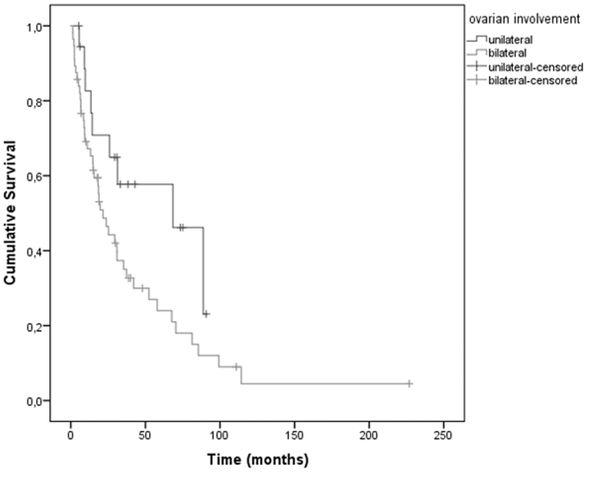

Figure 5. — Kaplan-Meier survival curves showing the effect of ovarian involvement on patients with ovarian metastasis ($p = 0.05$, log-rank test).

survival was similar ($p = 0.83$). Mean age was 52 ± 14 (range 23-84) years. Overall survival for all population was 49.2 months calculated from the diagnosis and 32.1 months from the gynecologic operation. Thirty-two (42.7%) patients were premenopausal and 43 (57.3%) patients were postmenopausal. When two groups were compared, the authors found that menopausal status did not change survival ($p = 0.272$). The primary sites were colorectal, endometrium, and gastric cancers. Comparison of median survival times for each primary tumor showed significant overall difference ($p < 0.001$). Median survival times for all cancers after surgery and after diagnosis were respectively, gastric 8.9 and 9.1 months, colorectal 25.3 and 31 months, breast 16.9 and 99.2 months, appendix 18.2 and 18.2 months, peritoneal mesothelioma 42.2 and 42.2 months, pancreaticobiliary 5.1 and 5.1 months, duodenum 2.5 and 2.5 months, and endometrium 67.4 and 67.4 months. After gynecologic surgery, patients with endometrial cancer, peritoneal mesothelioma, and colorectal cancer had the best survivals and may have had the best benefit from the treatment. Colorectal cancers had better survival than gastric tumors (Figure 3).

Postoperative chemotherapy was given to 65 (86.7%) patients and survival in patients who received chemotherapy was better than those who did not take chemotherapy (Figure 4). Mean survival was 34.6 months with chemotherapy

Table 2. — *Clinicopathologic characteristics of colorectal and appendiceal cancers.*

		n	%
Tumor site	Rectum	2	5.6
	Ascending colon	4	11.1
	Caecum	4	11.1
	Transverse colon	2	5.6
	Descending colon	4	11.1
	Appendix	10	27.8
	Sigmoid colon	5	13.9
	Rectosigmoid colon	5	13.9
Depth of invasion	T3	5	13.5
	T4	32	86.5
Ovarian involvement	Right	13	17.3
	Left	6	8.0
	Bilateral	56	74.7
Differentiation	Well differentiated	4	7.5
	Moderately differentiated	25	47.2
	Poorly differentiated	11	20.8
	Signet ring cell	13	24.5

group *vs*. 9.8 months in the other group ($p = 0.003$). Mostly used chemotherapy regimens were combinations of 5-flourouracil based oxaliplatin or irinotecan, paclitaxel-carboplatin, docetaxel, pemetrexed, cisplatin, and gemcitabine. Survival rates were compared for ovarian involvement. Of the patients, 74.3% had bilateral and 25.7% had unilateral ovarian metastasis. Bilateral metastasis was related with poor survival (Figure 5, 48.6 *vs.* 26.7 months, $p = 0.035$). The median ovarian tumor size was 9.7 (range 1-25) cm. Omental metastasis was detected in 56 (74.7%) patients and lymph node involvement in 43 (57.3%) patients. Omental metastasis and lymph node involvement also had with poor survival, but this was not statistically significant. Survival curves are shown in Table 2.

Colorectal and appendiceal tumors were the largest group in this study with 37 (49.3%) patients. All of them had extensive surgery and mean age was 52 ± 14.3 years. The vast majority were pathologically moderately differentiated (64.9%) and T4 tumors (86.5%) according to TNM classification. Survival was not different between differentiation groups ($p = 0.29$) and also between T3 and T4 tumor groups ($p = 0.69$) (Table 2).

In this study there were 12 patients with endometrial cancer metastatic to the ovaries. They were mostly postmenopausal (75%) and had other than endometrioid histologies (66.6 %), like clear cell and serous adenocarcinoma and grade 3 differentiation (75%) in pathology specimens. All patients were optimally debulked and staged comprehensively. Median survival was 67.4 months in the entire group of endometrial cancer patients.

Discussion

Gastric and colorectal cancers are the most common primary site in metastatic ovarian cancers and they are followed by breast cancer. Mechanism of metastasis to ovaries is not fully understood but it is thought that there may be three mechanisms including trans-coelomic, lymphogenous, and hematogenous pathways. Gastric tumors are more likely to cause retrograde lymphogenous and colon cancers are more likely to cause hematogenous metastasis [7]. In the present study the most common primary sites were colorectal and gastric cancers, respectively. Surgical approach to metastatic ovarian cancers are still controversial because there is no prospective randomized data in literature. In this study most of the patients had extensive surgery which included completely removal of gynecologic metastatic lesions with optimal debulking and resection of primary with regional lymph nodes. Wu *et al.* [8] reported that colorectal and gastric cancers are the most common primary metastatic tumors to the ovaries. The present authors found that colorectal and gastric tumors as the most common factors compatible with this previous study. According to the results, colon tumors were more frequent in both studies rather than rectum cancers which may be in consequence of radiotherapy or vascular circulation differences.

Several studies showed that primary tumor site is a good determinant of prognosis [4, 5, 8, 9]. In the present study calculated survival times for each primary cancer was significantly different. Best survival was seen in patients with endometrial cancers (67.4 months) although presence of histologic types with poor prognosis and followed by peritoneal mesothelioma (44.4 months). In the study of Brigand *et al.*, after cytoreductive surgery with hyperthermic chemotherapy, median survival was 37.8 months for peritoneal mesothelioma patients with residual nodules smaller than 2.5 mm, whereas it was 6.5 months for those had residual disease more than 2.5 mm [10]. The present authors believe that extensive surgery with comprehensive staging and effective chemotherapy regimens used in adjuvant setting has led to these good results. In this cohort, metastatic tumors of colorectal origin had better survival than gastric origin (25.3 *vs*. 8.9 months). This result was compatible with a previous retrospective study which was done by Jeung *et al.* [11]. They found that with cytoreductive surgery survival of colorectal cancers metastatic to the ovaries is better than that of gastric cancers (24 *vs*. 12.1 months, $p = 0.001$).

Rich ovarian blood supply in premenopausal period leads to hematogenous metastasis to the ovaries more often and it was reported that patients who had Krukenberg tumors were younger than primary epithelial ovarian cancer patients [9, 12]. However, in the present study 43 (57.3%) patients were postmenopausal and the mean age of 52 years is a little more than other studies. The present authors found that premenopausal status did not change the survival significantly. In agreement with previous results, ovarian involvement was a determinant of prognosis [9, 13]. Patients with unilateral ovarian involvement live longer than those with bilateral ovarian involvement. Shortened survival may be

related to more advanced and aggressive disease that can cause more disseminated metastasis. Likely omental involvement is an indicator of dissemination. The present authors confirmed that when patients detected omental involvement compared with those who do not, survival was better in non-involved population but that was not statistically significant (41 *vs.* 29 months $p = 0.082$). Interestingly, the present results showed that peritoneal washing fluid/ascites cytology or lymph node involvement have no effect on survival which can demonstrate the extent of disease.

With developments in chemotherapic drugs and the discovery of new targeted therapies, prolonged survival is observed in many cancer types. Endometrial cancer patients received paclitaxel and carboplatin chemotherapy regimen in the adjuvant setting as standard therapy. 5-flouracil based oxaliplatin and irinotecan regimens plus bevacizumab [14] or cetuximab/panitumumab [15] which were used in metastatic colorectal cancers may have beneficial effects on survival. There are many chemotherapy options used in metastatic breast cancer, but chemotherapy response rates fall in subsequent lines. After surgery 65 (86.7%) patients received chemotherapy and survival in patients who received chemotherapy was better than those who did not take. Ganesh *et al.* [16] reported that chemotherapy after surgery had a beneficial effect on overall survival but had no effect on progression free survival. However, the results of this study showed that median survival of breast cancer patients after diagnosis was 99.2 months and after gynecologic surgery it was 16.9 months. Bigorie *et al.* [17] reported that the median time between primary breast cancer diagnosis and the diagnosis of pelvic disease was five years. The present authors confirmed that survival of metachronous metastatic tumors was longer than synchronous metastatic tumors was supports that time to metastasis is a good prognostic factor. It is because limited disease has an interval between diagnosis and the development of dissemination. In previous reports [8, 11] there was also survival benefit in favor of metachronous metastatic ovarian tumors compatible with the present study. Patients that underwent extensive surgery had better survival than minimal surgery group but this was not statistically significant. Defining the minimal surgery as performing only TAH+BSO and low number of patients in minimal surgery may cause this nonsignificant result.

In conclusion, while the prognosis of the metastatic tumors to the ovaries is poor, achieving complete resection or optimal debulking surgery may improve survival in some histologic subgroups. Tumors originating from endometrial cancer, peritoneal mesothelioma, and colorectal cancer seems to be the best candidates for cytoreductive surgery. Timing of metastasis development, extent of disease, and chemotherapic options should be evaluated by experienced multidisciplinary team before operation. Prospective randomized future studies are needed to resolve this controversial issue.

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