Nongenital metastatic cancers of the ovary: A clinical analysis

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Summary

Objectives: The aim of this study was to outline the parameters affecting the extent and type of surgery for metastatic tumors of the ovary.

Material-method: The data of 34 operated patients diagnosed with metastatic tumors of the ovary at the Istanbul University, Medical Faculty Gynecologic Oncology Department between 1991 and 1999 were evaluated retrospectively. The patients were divided into two study groups according to the origin of the tumor: 1. Metastatic tumors of the ovary originating from the organs apart from the gastrointestinal system (MT-NonGIS), 2. Metastatic tumors of the ovary originating from the gastrointestinal system (MT-GIS). Survival rates were calculated in months from the time of ovarian surgical intervention to the date of last known data of patient status. Mean survival rates for the noncensored data were calculated by the Kaplan-Meier method and resulting curves were compared by the log-rank procedure. Statistical significance was determined at the level of 0.05.

Results: The survival rate for all cases was 24.21 months; the same rate was calculated to be 45.36 months for the MT-nonGIS group while it was 15.8 months for the MT-GIS group. When both groups were compared in terms of survival rates, the difference was significant (p: 0.0025, log rank: 9.14). Overall cumulative survival rates for 9, 14, 24 and 50 months were 61.59%, 50.05%, 41.7% and 11.58%, respectively. It was also found that surgery performed on patients in the MT-GIS group did not alter the survival rate but if peritoneal metastasis was observed during surgery, life expectancy for these cases was significantly less.

Conclusion: Although the number of patients included in our study was small, it is important because it gives us a clue about the type of surgery that should be performed in GIS-originating metastatic tumors of the ovary. Our study shows that aggressive surgery should be avoided in patients with peritoneal metastasis/spread.

Key words: Metastatic ovarian cancers; Peritoneal carcinomatosis; Debulking surgery.

Introduction

Metastatic tumors of the ovary may arise from a different spectrum of organs including thyroid, gastric, colon and gallbladder [1]. Unfortunately, common in all, is how these tumors metastasize to the ovary and how these tumors should be treated remains unresolved. Although the incidence of metastatic tumors of the ovary is not precisely known, most of the papers indicate it to be around a value between 6 and 30% depending on the type of diagnostic method used [2]. The diagnosis, as in our paper, may be confirmed by the help of surgery (performed for a pelvic mass or therapeutic castration) and autopsy. In addition there is no unity between gynecologists and other surgeons on the type of surgery performed and postoperative treatment options for these patients. Even though it is not very common, classification and treatment of metastatic tumors of the ovary are not well established.

The aim of this study was to outline the parameters affecting the extent and type of surgery for metastatic tumors of the ovary.

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Materials and Methods

The data of 34 operated patients diagnosed with metastatic tumors of the ovary at the Istanbul University Medical Faculty Gynecologic Oncology Department between 1991 and 1999 were evaluated retrospectively using both Gynecologic Oncology and Pathology Department archives. The microscopic slides of each patient were re-evaluated and the diagnosis was reconfirmed by the pathologists.

The patients were divided into two study groups according to the origin of the tumor:

1. Metastatic tumors of the ovary originating from the organs apart from the gastrointestinal tract (MT-NonGIS).

2. Metastatic tumors of the ovary originating from the gastrointestinal system (MT-GIS).

Both groups were analyzed in terms of differences at the age of diagnosis. Survival rates were calculated by using gynecologic oncology follow-up forms and the status of 32 of 34 patients was checked by phone and mail. One of the two patients that could not be reached was in the MT-GIS group and she had died during the early postoperative period (first 12 weeks after the operation) due to a myocardial infarction. Another patient in the MT-GIS group was also unreachable.

Different chemotherapeutic regimens were applied to the patients: patients with carcinoma of the colon and breast mainly received agents like mitomycin, 5-fluorouracil and also hormonal therapy. Some patients received radiotherapy along with chemotherapy. Due to the high number of different protocols applied to the patients, we evaluated whether adjuvant chemotherapy had a positive effect on survival.

The surgical protocols were grouped and analyzed in three groups outlined below:

1. Total abdominal hysterectomy (TAH) + Bilateral salpingo-oophorectomy (BSO) + Surgical staging.
2. Total abdominal hysterectomy (TAH) + Bilateral salpingo-oophorectomy (BSO) + Surgical staging + Debulking surgery.
3. Biopsy or minimal surgery like BSO.

As mentioned above, since our study is mainly a clinical one, we avoided the term "Krukenberg" both during classification and estimation of survival rate.

The effect of histopathologic grade and persistence of peritoneal metastasis on prognosis was only evaluated in the MT-GIS group, since this group had significantly enough patients.

For all patients, survival rates and differences between the two groups, and effect of different surgical protocols, presence of ascites, laterality of the tumor and adjuvant therapy on prognosis were examined. In the MT-GIS group, differences in survival rates of gastric and colonic tumors were considered, and whether histologic grade, extent of surgery performed and presence of carcinomatosis peritonei had an effect on survival rates in this group of tumors.

Data were recorded using Microsoft Access 97 and statistical calculations were performed by SSPS 8.0 for Windows. Survival rates were calculated in months from the time of ovarian surgical intervention to the date of last known data on patient status. Mean survival rate for the noncensored data was calculated by the Kaplan-Meier method and resulting curves were compared by the log-rank procedure. Statistical significance was determined at the level of 0.05.

Results

Data of 497 patients who were diagnosed with malignant ovarian carcinoma in the Istanbul University Medical Faculty Department of Gynecologic Oncology were examined. Ninety-two of 497 patients (18.5%) had malignant non-epithelial ovarian carcinoma and 44 (47.8%) of them (8.8% of all patients) were diagnosed as having metastatic tumors of the ovary. Among 44 patients with metastatic tumors, in ten the tumor originated from other genital organs (22.7%) and in the rest the origin was extragenital (77.3%). Extragenitally-originating tumors comprised 6.8% (34/497) of all tumors and 37% of non-epithelial tumors.

The ages of patients with extragenitally-originating tumors varied between 19 and 77 (median 40, mean 41.82). There was no difference between the mean ages of both groups (41.92±10.94 MT-nonGIS vs. 41.77±12.88 MT-GIS, t=0.034 p=0.973). The most frequent complaint was fullness in the abdomen in the MT-GIS group. In three patients with breast cancer and two patients with colon cancer, ovarian masses were detected during routine gynecologic controls.

Of 34 extragenitally-originating metastatic tumors of the ovary, 12 originated from the colon, eight from the stomach, one from the rectum and seven from the breast. Among patients with gastric carcinoma, only one was preoperatively diagnosed. Four of the patients with colonic primaries were previously operated on for colon cancer. Time interval between the first surgery involving the primary tumor and surgery for adnexal pathology was 15 ± 4.96 months for colon carcinoma and 63.29 ± 9.39 months for breast cancer. Types of tumors metastasizing to the ovary are detailed in Table 1.

The survival rate for all cases was 24.21 months (SE-standard error): 3.86, 95% CI (confidence interval): 16.65-31.78); the same rate was calculated as 45.36 months (SE 7.18, 95% CI: 31.28-59.43) for the MT-nonGIS group while it was 15.8 months (SE 2.31, 95% CI: 11.27-20.33) for the MT-GIS group (Table 2). When both groups were compared in terms of survival rates the difference was significant (p: 0.0025, log-rank: 9.14) (Table 3, Figure 1). Overall cumulative survival rates for 9, 14, 24 and 50 months were 61.59%, 50.05%, 41.7% and 11.58%, respectively. For the MT-nonGIS group cumulative survival rates were 71.11% for 28 months and 35.56% for 50 months. These rates were much lower in the MT-GIS group: 40.48% for 13 months and 25.3% for 24 months.

Table 1. — *Malignant tumors metastatic to the ovaries. (**There are no available survival data on two patients).*

	MT-NonGIS*				MT-GIS*				
Primary tumors	Breast	Liver	N.H. Lymphoma*	V.M. Melanoma*	Gastric	Colon	Rectum	Undetermined	Total
Total	7	1	3	1	8	12	1	1	34
Laterality									
Unilateral	1	1	2	1		4	1		10
Bilateral	6		1		8	8		1	24
Sugery									
1. TAH+BSO+SS*	7	1	2	1	4	3	1		19
2. TAH+BSO+SS+Debulking			1		3	6			10
3. Biopsy					1	3		1	5
Chemotherapy									
(+)	5	1	3	1	4	8	1	1	24
(–)	2				4	4			10
Ascites									
(+)	3	2			5	5	1	1	17
(–)	4	1	1	1	3	7			17

*MT-Non GIS: Metastatic ovarian tumors arising from the non-gastrointestinal system, *MT-GIS: Metastatic ovarian tumors arising from the gastrointestinal system, *N.H.Lymphoma: Non Hodgkin's lymphoma, *V.M. Melanoma: Vulvar malignant melanoma, *TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, SS: Surgical staging.

Table 2. — *Survival analysis of patients with malignant tumors metastatic to the ovaries (Kaplan Meier method) (SE = Standard Error - 95% CI = 95% Confidence Interval).*

Survival parameters for extragenital metastatic ovarian tumors	Mean (months)	SE 95% CI	Median (months)	SE 95% CI	n (%)
Overall survival for extragenital metastatic ovarian tumors	24.21	3.86/16.6-31.7	23	7.26/8.7-37.2	32
Metastatic ovarian tumors arising from Non-GIS*	45.36	7.18/31.2-59.4	50	16.52/17.6-82.3	11 (27%)
Metastatic ovarian tumors arising from GIS	15.8	2.31/11.2-20.3	13	1.55/9.9-16.04	21 (51%)
Laterality of ovarian involvement					
Unilateral	27.50	4.20/19.2-35.7	25	1/23.04-26.9	9 (28%)
Bilateral	22.36	4.4/13.6-31.07	13	1.94/9.2-16.8	23 (72%)
Type surgery					
TAH+BSO+SS**	29.50	6.05/17.6-41.35	14	11.3/.00-36.2	19 (59%)
TAH+BSO+SS+Debulking	19.48	4.15/11.3-27.6	24	10.17/4.06-43.9	9 (28%)
Biopsy	15.75	4.82/6.3-25.2	9	8.5/.00-25.6	4 (13%)
Adjuvant chemotherapy status					
(+)	30.07	4.84/20.5-39.5	25	1.85/21.3-28.6	24 (75%)
(–)	10.38	2.28/5.9-14.8	9	0.41/8.2-9.8	8 (25%)
Ascites					
(+)	21.76	4.86/12.2-31.2	13	3.15/6.8-19.1	17 (53%)
(–)	23.64	4.01/15.7-31.5	25	10.6/4.2-45.7	15 (47%)
Survival parameters for extragenital metastatic ovarian tumors arising from GIS					
Type of surgery					
TAH+BSO+SS*	11.38	1.9/7.6-15.09	9	0.68/7.6-10.3	8 (38%)
TAH+BSO+SS+Debulking	19.48	4.15/11.3-27.6	24	10.1/4.06-43.9	9 (43%)
Biospy	15.75	4.8/6.3-25.2	9	8.5/.00-25.6	4 (19%)
Histopathological grade of tumors					
Grade II	16.9	3.56/9.1-23.05	23	8.54/6.2-39.7	7 (33%)
Grade III	15.21	2.77/9.7-20.6	9	1.87/5.3-12.6	14 (67%)
Peritoneal disease (carcinomatosis peritonei)					
(+)	11.58	1.96/7.7-15.4	22.24	4.2/13.8-30.5	12 (57%)
(–)	9	0.41/8.2-9.8	25	3.87/17.4-32.5	9 (43%)

*GIS: Gastrointestinal system, **TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, SS: Surgical staging.

There was enough information about survival rates of 32 patients. In four of the cases, surgery was not carried out and only open biopsies were taken. In ten of the 34 cases, the tumor was unilateral and in the rest bilateral. When study groups were compared, lateralization did not affect survival rates. In addition, surgical technique (Figure 2) and presence of ascites did not affect the prognosis significantly (Table 3). However adjuvant therapies altered the survival rates significantly. The survival rate of patients who received adjuvant therapies were significantly longer (Table 3, Figure 3).

In the MT-GIS group, survival rates of patients with

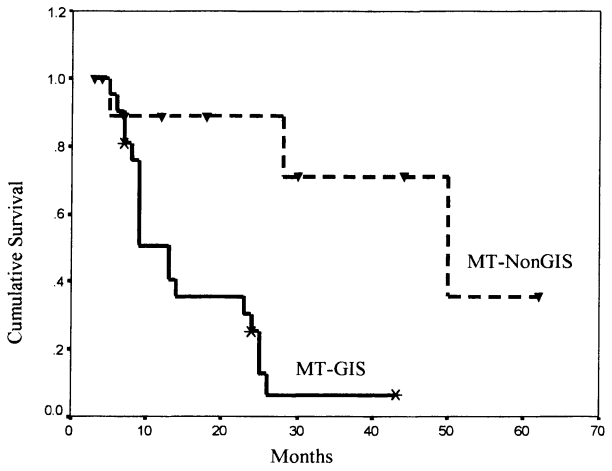

Figure 1. — Survival time difference between the two study groups (p=0.0025). MT-GIS: Metastatic ovarian tumors arising from the gastrointestinal system. MT-NonGIS: Metastatic ovarian tumors arising from the non-gastrointestinal system.

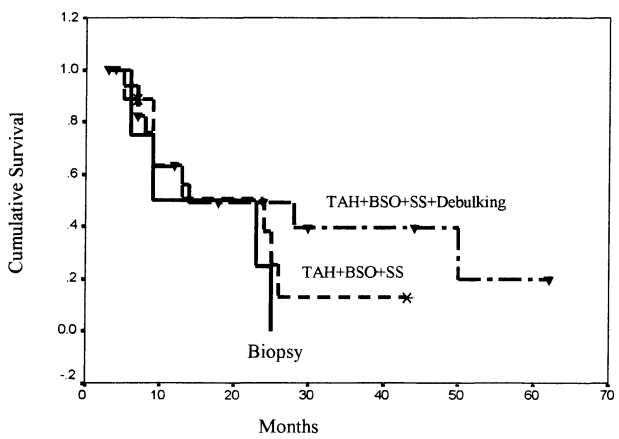

Figure 2. — The effects of different types of surgery on survival rates (p=0.3405). TAH: Total abdominal hysterectomy. BSO: Bilateral salpingo-oophorectomy. SS: Surgical staging.

Table 3. — *Significant difference between survival curves of variables (by log-rank test along with Kaplan Meier analysis) (* = Significant).*

Variables of extragenital tumors	Log-rank	p
MT-NonGIS vs. MT-GIS	9.14	0.0025*
TAH+BSO+SS** vs. TAH+BSO+SS+Debulking vs. Biospy	2.15	0.3405
Bilateral vs. unilateral ovarian involvement	1.17	0.2804
Adjuvant chemotherapy status (+) vs. (–)	9.24	0.0024*
Ascites (+) vs. (–)	0.95	0.3290
Variables of MT-GIS Group**	**Log-rank**	**p**
Survival time of gastric tumors vs. colon tumors	8.38	0.0038*
Grade II vs. grade III	0.01	0.9075
Peritoneal disease (carcinomatosis peritonei) (+) vs. (–)	3.92	0.0476*
TAH+BSO+SS* vs. TAH+BSO+SS+Debulking vs. Biopsy	2.32	0.3130

*GIS: Gastrointestinal system, **TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, SS: Surgical staging, MT-GIS: Metastatic ovarian tumors arising from gastrointestinal system.

gastric cancer were significantly lower when compared to patients with colon cancer (Table 3). The pathologic diagnosis of Krukenberg tumor was made for seven of eight gastric and five of 13 colon cancer patients. There were no grade I tumors in the MT-GIS group, rather all were graded as either II or III and there was no difference in prognosis between these grades (Table 3). It was also found that surgery performed on patients in the MT-GIS group did not alter the survival rate but if peritoneal metastasis was observed during surgery, life expectancy for these cases was significantly lower (Table 3, Figure 4).

Discussion

The incidence of metastatic tumors of the ovary varies between 6-30% in most studies. This percentage was calculated to be 8.8% for all metastatic tumors and 6.8% for non-GIS originating tumors in our study. In contrast to primary ovarian carcinoma, metastatic tumors of the ovary are diagnosed at an earlier age. Primary ovarian carcinoma is seen between 65 and 85 years, while metastatic tumors are seen at a younger age. The mean age of diagnosis in our study was 41.8 years. Metastatic tumors of the ovary are mostly gastrointestinal in origin. Colorectal carcinoma is especially misdiagnosed as ovarian carcinoma since both are located in the pelvis. This is a good example of the difficulties encountered during the differential diagnosis of pelvic tumors.

We examined the effects of laterality, presence of ascites, adjuvant therapy and surgical technique on survival in all cases and have seen that apart from adjuvant therapy none of them significantly affected the length of survival. Some authors believe that metastatic tumors of the ovary should be evaluated as a whole [2] and they, like we did, evaluated the effect of some parameters in all of the cases. However, one must bear in mind that the behaviour of the metastatic tumor is dependent on the type of primary tumor. An important example is GIS-originating tumors which behave very aggressively. Hence, we believe that when studying metastatic tumors of the ovary, at least GIS-originating tumors should be evaluated separately.

Most of the extragenital metastatic tumors of the ovary are gastrointestinal in origin. In our study we calculated this ratio as 65%. An interesting point is that there is no consensus about what is to be done surgically after gastrointestinal origin of the metastatic tumor of the ovary is confirmed during an operation. The type and extent may be decided after uncovering the paths used by the primary tumor when metastasizing to the ovary. A study done by Chang and colleagues is helpful in answering this question [3]. These researchers found that GIS-originating tumors primarily metastasize by the lymphatics to the ovaries and their hypothesis was supported by the works of Hirono and Maehara. Hirono, in a study on 30 patients with primary gastric tumors, hypothesized that metastatic tumor cells carried by the lymphatics are

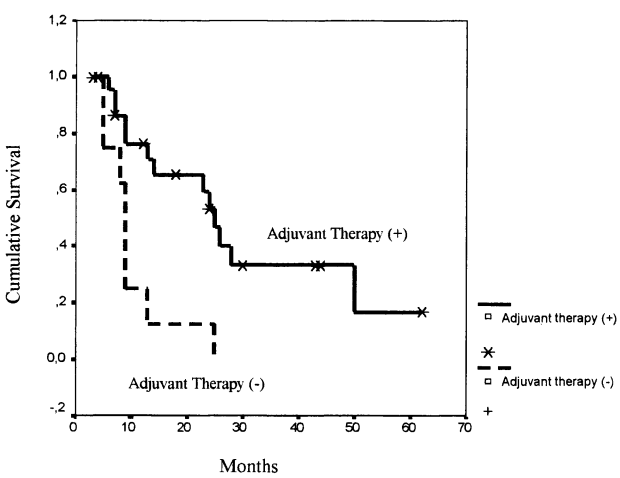

Figure 3. — Comparison of survival time with adjuvant therapy (+) and (–) groups (p=0.0024).

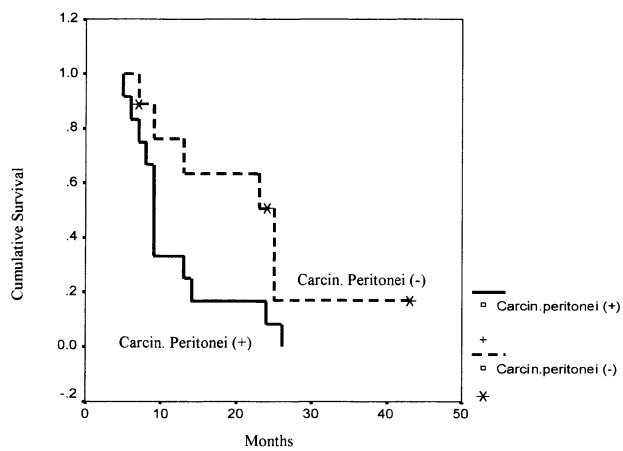

Figure 4. — The difference in survival time of carcinomatosis peritonei (+) and (–) patients (p=0.0476).

first seen at the hilus of the ovary [3]. Maehara and colleagues demonstrated that nodal metastasis was an independent risk factor for peritoneal metastasis in a series of 1,108 patients [4]. The findings by Chang *et al.* [3] support those of Maehara *et al.* The author in this study claims that in cases with peritoneal metastasis, ovarian metastasis occurs via the lymphatics. In our study we showed that in patients with peritoneal metastasis, length of survival was significantly shortened. This finding is followed by a question: Should we perform aggressive surgical treatment in patients with peritoneal metastasis? Petru and colleagues in a series of 82 patients with extragenital metastatic tumors of the ovary have shown that aggressive surgical treatment in patients with colon cancer as the primary tumor significantly improves survival rates [5]. Hence to sum up, we can presume that metastasis by way of the lymphatics is present in GIS-originating tumor cases with peritoneal metastasis and in these cases, survival rates are diminished. These findings are in accord with the idea that in patients with peritoneal spread, aggressive surgery will not improve survival rates. However, in patients with colon cancer without peritoneal spread, aggressive surgery seems to improve survival rates.

The main reason for the difference between the survival rates of patients with primary gastric and colorectal tumors is the different response rates of these tumors to adjuvant therapies. Colorectal tumors, in contrast to gastric, are more likely to have a good response to adjuvant chemotherapy. Therefore, in patients without peritoneal metastasis, removal of the tumor increases the response rates to chemotherapy. In patients with peritoneal metastasis and Stage IV disease, response rate to chemotherapy is diminished.

In our study, cancer of the breast was the second most commonly encountered tumor, after GIS-originating tumors, among metastatic tumors of the ovary (21%, 7/34). In a study of 513 patients by Fujiwara and colleagues, the rate of metastatic tumors of the ovary was found to be 19.2%. In the same series, cancer of the breast was again the second most common primary tumor seen accounting for 22.9% of the metastatic tumors [6]. In a study by Curtin and colleagues, 230 breast cancer patients who underwent oophorectomy due to a number of different reasons were examined [7]. Curtin stated that the chances of an adnexal mass being discovered in a breast cancer patient is much more likely to be a new primary tumor or an ovarian carcinoma when compared to the normal population. The study stresses the importance of surgical exploration in breast cancer patients with adnexal masses [7].

Conclusion

Although the number of patients included in our study is small, it is important because it gives us a clue about the type of surgery that should be performed in GIS-originating metastatic tumors of the ovary. Our study shows that aggressive surgery should be avoided in patients with peritoneal metastasis. We must add that in forthcoming studies concerning metastatic tumors of the ovary, cases should be homogenized and the effects of more and different parameters on survival should be evaluated for each type of tumor.

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