Preoperative evaluation, clinical characteristics, and prognostic factors of nongenital metastatic ovarian tumors: review of 48 patients

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Summary

Objective: To evaluate the clinicopathologic characteristics, methods for preoperative evaluation, prognostic factors, and overall survival of nongenital ovarian metastases (NGOM). *Material and Methods:* Forty-eight patients with NGOM followed between January 2001 and January 2009 in Cukurova University Department of Gynecologic Oncology were included in the study. Clinical characteristics including demographics, preoperative imaging methods, endoscopic evaluations, tumor markers, histopathologic findings, prognostic factors, types of surgery, modalities for adjuvant therapy and survival were analyzed. *Results:* The gastrointestinal tract is the most common location of the primary tumor; colonic origin was found in 41% of the patients (n = 20). All metastatic lesions were adenocarcinoma with 23% of these classified as Krukenberg and 29% as mucinous type adenocarcinoma. When the whole group was evaluated, median survival time was 15.7 months in patients and there were significant differences between the groups according to primary site. Histopathological subtypes and presence of peritoneal carcinomatosis affected the median survival. The significant prognostic factors were primary site and histopathologic subtypes of the NGOM. *Conclusions:* NGOM should be kept in mind to avoid inappropriate management and therapy in patients with surgically managed ovarian tumor, especially young patients with gastrointestinal complaints.

Key words: Nongenital ovarian metastases; Prognostic factors; Preoperative evaluation; Survival.

Introduction

The ovaries represent the common site for genital metastatic disease. Gastrointestinal tumors and breast cancers are the most common sources of nongenital ovarian metastases (NGOM) [1-3]. Krukenberg tumors are metastatic tumors of the ovary and histopathologically this term describes signet ring cell adenocarcinoma. Stomach and colon/rectum carcinomas are the most common primary sites of Krukenberg tumors [1]. Occasionally hematologic malignancies and other solid tumors involve the ovaries [2]. There are several ways for metastases to the ovary; in addition to direct spread, lymphatic and hematogenous spread and transcoelomic dissemination are common routes [3].

The accurate preoperative evaluation of NGOM is very important as the misinterpretation of these tumors may cause inappropriate management and unnecessary surgery. There is insufficient information on the outcome of patients with NGOM who undergo surgery and cytoreduction [4-7]. Some authors suggest the beneficial effect of surgery especially in cases with colorectal cancer but the role of cytoreduction and surgical strategy is not clear enough [4-7]. Therefore, preoperative evaluation of these tumors is important. Imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used in daily practice. Gynecologic oncologists must consider the Krukenberg tumor when there are gastrointestinal symptoms and bilateral ovarian tumors, and preoperative screening must be complete [8, 9].

The aim of this study was to evaluate and discuss the preoperative clinical findings, surgical approach and prognosis in patients with NGOM.

Material Methods

Forty-eight patients with NGOM were identified during surgery between January 2001 and January 2009 at Cukurova University, Department of Gynecologic Oncology. Patient records were reviewed regarding the following data: age, menopousal status, main complaint, primary site, chronology, preoperative tumor markers such as CA 125, carcinoembriologic antigen (CEA), and CA 19-9, preoperative gastrointestinal endoscopic evaluation, imaging methods such as CT and MRI. Operative findings: presence/absence of ascites, bilaterality, tumor size, peritoneal carcinomatosis, residual tumor status, primary sites, surgical treatment modalities and additional surgical procedures including appendectomy, bowel resection, and cholecystectomy were noted. Adjuvant therapy modalities: chemotherapy and/or radiotherapy and survival data were reviewed.

Surgical treatment modalities were catogorized as 1 - Oophorectomy or ovarian biopsy; 2 - Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO); 3 - TAH+BSO+omentectomy, 4 - TAH+BSO+omentectomy+ bilateral pelvic and paraaortic lymphadenectomy (BP-PALND)+cytoreduction such as peritonectomy. Optimal cytoreduction was the term used if the diameter of the largest residue tumor was less than 1 cm. Survival was determined based on the date of surgery to the date of last follow-up or death. The follow-up was censored on September 2011.

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Table 1. — *Demographic characteristics and clinical findings of the patients.*

	Stomach cancer (n = 10)	Colorectal cancer (n = 19)	Breast cancer (n = 5)	Appendiceal cancer (n = 3)	Gallbladder cancer (n = 2)	Pancreatic cancer (n = 1)	Unknown primary (n = 7)	Total	*p*
Age (mean ± SD)	43.9 ± 12.7	46.5 ± 12.7	48.2 ± 3.2	67 ± 14.7	40 ± 12.0	35.0	68.1 ± 8.6	50.1 ± 14.4	0.001
Menopausal status (n)									
Premenopausal	7	11	1	1	1	1	1	23 (48%)	0.208
Postmenopausal	3	9	4	2	1	–	6	25 (52%)	
Presenting symptoms (n)									
Abdominal pain	2	5	1	0	0	1	5	14 (29%)	0.136
Abdominal distention	3	4	3	3	1	0	1	15 (31%)	
Abdominopelvic mass	3	4	0	0	1	0	1	9 (18)	
Abnormal uterine bleeding	0	1	0	0	0	0	0	1 (2%)	
Dyspeptic complaints	2	6	1	0	0	0	0	9 (18%)	
Tumor markers (median)									
CA 125 U/ml	118.0	119	247	259	105	121	234	146.5	0.560
CEA ng/ml	10.4	5.2	4.1	25	19.5	19	3.4	6	0.413
CA 19-9 U/ml	17.5	75.5	10.3	30	16.9	45	179.5	32	0.857
Imaging methods (n)									
CT	6	11	5	1	2	0	4	29 (60%)	0.672
MRI	1	2	0	1	0	0	1	5 (10%)	
GI endoscopic evaluation (n)									
Not done	7	12	4	1	1	0	2	27 (56%)	0.405
done	3	8	1	2	1	1	5	21 (44%)	

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS version 16.0; SPSS Inc., Chicago, IL, USA). Data are shown as mean ± SD and propriety data are shown as median, min-max value. The chi-square test for cross-tables and one-way ANOVA for comparing variables between the primary site groups were used. Survival data were computed using the Kaplan-Meier method. Differences in the survival curves were calculated using the log-rank test. The Cox proportional hazard model was used to assess the significance of multiple variables.

Results

There were 456 cases surgically identified with ovarian cancer in the study period in our institute. NGOM cases accounted for 10.5%; the mean age of the patients was 50.1 ± 14.1 years. There were stastistically significant differences observed between the primary site of the NGOM according to mean age (p = 0.001). Of patients 48% were premenopausal and 52% were postmenopausal and no differences were found between the groups. The most common presenting symptoms were abdominal distension (31%). Dyspeptic complaints were dominant in nine patients (18%). Primary tumor preceeded metastatic ovarian lesions in 33% of the patients and all cases with breast cancer were in this group. In two-thirds of the patients NGOM were detected during the exploration of a pelvic mass. Preoperative gastrointestinal endoscopic evaluation had been performed in 43% of the patients. Preoperative radiological imaging had been done in 70% of patients. Tumor diameter was between 6 and 10 cm in 48% of the patients and larger than 10 cm in 23% of the patients. Seventy-seven percent of the patients had bilateral ovarian masses. Thirteen percent of the patients had ascites more than three liters. Peritoneal carcinomatosis was found in 40% of the patients. The demographic characteristics and clinical findings of the patients are presented in Table 1.

Minimal surgical effort including ovarian biopsy or oophorectomy had been performed in 27% of the patients and TAH+BSO+BPPALND+cytoreduction had been done in 15% of the patients. Colon resection was performed in 42% of all patients and cytoreductive surgery for colorectal cancer had been done in 17 patients. Major surgical complications occurred in 12% of the patients. Histologically all metastatic lesions were adenocarcinoma with 23% of these classified as Krukenberg and 29% as mucinous type adenocarcinoma. Adjuvant chemotherapy had been given to 83% of the patients and 14% of the patients received radiotherapy. Intraoperative findings, histopathologic characteristics, types of surgery, adjuvant treatment modalities, and survival times of the patients are presented in Table 2. The gastrointestinal tract, especially the colon, was the most common origin of NGOM (41%). Origin of the tumor was not found in 14% of the cases (n = 7).

Survival rates were compared for primary site, bilaterality, presence of peritoneal carcinomatosis, types of operation, additional surgical procedures, histopathologic subtypes and modalities used for adjuvant aims. Median survival times were different according to the primary site (p = 0.001) and median survival time was 15.7 months. The longest survival was found in cases with colorectal cancer; it was 23 months. The shortest survival was found in cases with gastric cancer (7 months). Median overall survival time was 22 months in cases with breast cancer and eight months in cases with unknown primary. Log rank analysis showed that bilaterality of NGOM, surgery types, additional surgery procedures and adjuvant therapy modalities did not affect sur-

Table 2. — *Intraoperative findings, histopathologic characteristics, types of surgery, adjuvant treatment modalities, and survival times of the patients.*

	Stomach cancer (n = 10)	Colorectal cancer (n = 19)	Breast cancer (n = 5)	Appendix cancer (n = 3)	Gallbladder cancer (n = 2)	Pancreas cancer (n = 1)	Unknown primary (n = 7)	Total	*p*
Chronology									
Synhronous	7	13	0	3	1	1	7	32 (67%)	0.015
Metachronous	3	7	5	0	1	–	–	16 (33%)	
Laterality									
Unilateral	1	5	0	1	1	0	3	11 (23%)	0.498
Bilateral	9	15	5	2	1	1	4	37 (77%)	
Tumor diameter									
1-5 cm	2	5	3	2	0	1	1	14 (29%)	0.621
6-10 cm	6	10	1	1	1	0	4	23 (48%)	
> 10 cm	2	5	1	0	1	0	2	11 (23%)	
Ascites									
Absent-minimal	1	11	0	2	0	0	4	18 (37%)	0.273
1-3 l	5	8	4	1	1	1	3	23 (48%)	
> 3 l	3	1	1	0	1	0	0	6 (13%)	
Peritoneal carcinomatosis									
Absent	4	16	2	2	1	1	3	29 (60%)	0.275
Present	6	4	3	1	1	0	4	19 (40%)	
Surgery types (n)									
1	6	5	0	0	1	0	1	13 (27%)	0.094
2	0	4	1	0	1	0	3	9 (19%)	
3	3	6	4	3	0	1	2	19 (39%)	
Additional surgery procedure									
Not done	4	2	5	0	0	1	1	13 (27%)	0.001
Appendectomy	0	1	–	2	0	0	0	3 (6%)	
Colon resection	0	17	–	1	0	0	2	20 (42%)	
Splenectomy	1	0	–	0	0	0	0	1 (2%)	
Cholecystectomy	0	0	–	0	2	0	1	2 (4%)	
Another	5	0	–	0	0	0	4	9 (19%)	
Residuel									
Optimal cytoreduction	1	14	4	3	1	1	5	29 (60%)	0.108
≥ 1 cm	9	6	1	0	1	0	2	19 (40%)	
Complication									
Absent	10	17	3	3	2	1	6	42 (87%)	0.277
Bowel	0	0	1	0	0	0	0	1	
Urinary tract	0	3	0	0	0	0	1	4	
Incision comp	0	0	1	0	0	0	0	1	
Infection	0	0	0	0	0	0	0	0	
Another	0	0	0	0	0	0	0	0	
Histopathologic subgroup									
Krukenberg	6	3	0	0	0	0	2	11 (23%)	0.003
Musinous	2	9	0	3	0	0	0	14 (29%)	
Other Adenocancer	2	8	5	0	2	1	5	23 (48%)	
Chemotherapy									
Not done	1	5	0	1	0	0	1	8 (17%)	0.737
Done	9	15	5	2	2	1	6	40 (83%)	
Radiotherapy									
Not done	10	16	2	3	2	1	7	41 (86%)	0.048
Done	0	4	3	0	0	0	0	7 (14%)	
Survival (months)									
Median ± SD (95% CI Lower-upper bound)	7 ± 1.4 (4.1-9.8)	23 ± 6.5 (10.2-35.7)	22 ± 0.0	6 ± 2.4 (1.1-10.8)	4.5	2	8 ± 5.8 (0.0-19.5)	15.7 ± 12 (8.2-15.7)	0.001

vival (Table 3). Multivariate analysis showed that histopathological subtypes and presence of peritoneal carcinomatosis affected the median survival. However age, the presence of peritoneal carcinomatosis, types of surgery, and optimal cytoreduction were not found to be prognostic factors in NGOM (Table 4).

Discussion

Metastatic ovarian cancers are not rare. In clinical and autopsy series, 5-20% of patients with primary ovarian cancers present with metastatic ovarian malignancies [1]. Generally, these rates include both genital and nongenital ovarian tumors. Moore *et al*. [3] demonstrated an 8.2%

Table 3. — *Survival analysis of NGOM*.

	Median survival (months) ± SD	95% CI (lower-upper bound)	*p*
Bilaterality			
Unilateral (n = 11)	15 ± 6.1	2.8-21.1	0.254
Bilateral (n = 36)	12 ± 1.9	8.1-15.8	
Overall	12 ± 1.9	8.2-15.7	
Peritoneal carcinomatosis			
Present (n = 19)	8 ± 2.7	2.5-13.4	0.046
Absent (n = 28)	15 ± 4.3	6.4-23.5	
Surgery type			
1 (n = 13)	7 ± 2.3	2.3-11.6	0.782
2 (n = 9)	12 ± 3.5	4.5-19.0	
3+4 (n = 26)	12 ± 2.9	6.1-17.8	
Overall	12 ± 1.9	8.2-15.7	
Additional surgery procedure			
Colon resection (n = 20)	14 ± 2.2	9.6-18.3	0.17
Overall	12 ± 2.8	6.5-17.5	
Histopathologic type			
Krukenberg (n = 11)	4 ± 0.3	3.2-4.7	0.001
Mucinous adenocarcinoma (n = 14)	13 ± 2.8	7.5-18.5	
Other adenocarcinoma (n = 23)	14 ± 5.4	3.3-24.6	
Overall	12 ± 1.9	8.2-15.7	
Adjuvant therapy			
Chemotherapy			
Done (n = 40)	12 ± 2.8	6.3-17.6	0.467
Not done (n = 8)	12 ± 6.1	0.0-24.0	
Radiotherapy			
Done (n = 6)	13 ± 16	0.0-44.3	0.117
Not done (n = 42)	12 ± 1.9	8.2-15.7	

Table 4. — *Multivariate analysis of NGOM*.

(No. 48)	*p*	HR	95% CI (lower-upper bound)
Age (ref. 49)	0.355	0.671	0.2-1.5
Primary site (ref unknown)	0.001		
Stomach	0.011	0.187	0.05-0.067
Colorectal	0.001	0.109	0.035-0.344
Breast	0.019	0.146	0.029-0.727
Peritoneal carcinomatosis	0.961	0.976	0.371-2.566
Surgery procedure (ref 1)	0.236		
2	0.232	2.25	0.594-8.550
3+4	0.919	0.941	0.369-21.641
Optimal cytoreduction	0.509	2.827	0.369-21.641
Histopathologic subtypes	0.046	3.843	1.023-14.438

Ref: referance variable, HR: hazard ratio, CI: confidence interval.

incidence of metastases to the ovary in patients who were thought to have a primary ovarian tumor. Detection of NGOM in gynecologic surgery has been found to be a poor prognostic indicator in a large population study with a long follow-up [10]. An important finding of this study was that in more than half of the cases with NGOM, it originated from the gastrointestinal tract. de Waal *et al*. [11] reported that ovarian metastases mimicking primary ovarian tumor originated from the large intestine in one fourth of the cases. In another study gastrointestinal origin was found in 42% of the cases [12]. Fusiwara *et al*. found that gastric primaries metastasing to the ovary made up 30% of the cases and this was followed by breast (21.6%), and colon cancers (6.7%) at the time of autopsy [13]. An explanation for this discrepancy may be the global incidence of stomach cancer. In our study identified NGOM cases consisted of 10.5% of the surgically managed ovarian cancers in the study period, and colorectal malignancies were the most common site for NGOM. This is followed by malignancies of the stomach, breast, and unknown primary site. These results are consistent with the literature [3-5]. Synhcronous NGOM was found in 32 patients (66%) in our study. This high persentage indicates the importance of preoperative evaluation; 16 patients had metachronous NGOM.

The radiological features of metastatic ovarian cancers show considerable variability due to primary site [8]. Unfortunately, radiologically there are no definitive criteria for the differentation of primary and metastatic ovarian tumors. In general, metastatic ovarian tumors present with bilateral ovarian involvement and more solid appearance while primary ovarian tumors show unilaterality and cystic nature. The shape of ovarian metastasis from colon cancer tends to be cystic, thus a solid and cystic nature cannot be an absolute milestone for the diagnosis in these metastatic cancers [9]. In our study, among the preoperative imaging modalities CT and MRI were used in 60% and 10% of the patients, respectively. Colorectal, appendiceal, and upper gastrointestinal tract primary tumors have been shown to be the most common primary malignancies associated with clinical findings suggestive of a primary ovarian cancer [2, 10, 11]. In our study preoperative endoscopic evaluation of the gastrointestinal tract had been performed in approximatelly half the patients (44%); an important point for clinical practice in that incomplete preoperative evaluation causes unnecessary surgery. In our cases the most common presenting complaints were abdominal distention and abdominal pain and dyspeptic symptoms (such as constipation, weight loss, nausea and vomiting). Therefore a detailed history is very important as seen in all other clinical conditions. There were no differences for preoperative tumor marker levels according to the primary site in our study. The median serum CA 125, CEA and CA 19-9 were 146.5 U/ml, 6 ng/ml and 32 U/ml, respectively. However an elevated level of CEA may suggest gastrointestinal malignancy as the primary site [12].

The majority of metastatic ovarian tumors arise between the age of 40 and 60, and the mean age has been found to be ten years younger than that of patients with primary ovarian cancer. There are some explanations for this finding. Miller *et al*. [14] suggest that higher blood flow to the ovary in premenopausal women may increase the risk of metastatic disease to the ovary. In our study mean age of the cases was 50.1 years and menopausal status (48% premenopausal) was similar to other series. As an interesting finding, age was not found to be a prognostic factor in multivariant analysis. This result can be explained as heterogenity of the cases by primery site with different aggressiveness of the tumors.

NGOM is commonly bilateral in 60% of the patients and

frequently present in smaller sizes than primary ovarian cancer. In this series, bilaterality was found in 77% of the patients and only 29% of the cases had less than 5 cm tumor diameter. Approximately a quarter of the patients had larger than 10 cm tumor. These results are in conflict with the literature because NGOM are usually smaller than primary ovarian cancer. Fusiwara *et al*. reported 75% of metastatic ovaries had diameters less than 5 cm in their autopsy series [13]. Such conflict was explained in that this study was retrospective and consisted of surgically identified NGOM, however the literature (aforementioned study) data were based on autopsy findings. The bilaterality, size and amount of the ascites were not different for the primary site of NGOM in our study. This may be due to the limited number of cases analyzed in our study.

It is accepted that NGOM has a poor prognosis. However there is a significant difference in survival according to the primary site [15]. The longest median survival time has been found in patients with colorectal cancer and this was followed by breast cancer in our study which is compatible with the literature [4-7]. In our study, overall median survival was 15.7 months which is compatible with previous studies. Surgery is frequently indicated to detect the origin of an ovarian mass, and also for relief of symptoms in most cases. There are discordant results regarding the role of surgical resection or tumoral debulking in patients with NGOM. Some of these studies showed that the prognosis was better in patients undergoing complete surgical resection, especially in cases with colorectal cancers [4, 7, 16, 17]. However some researchers suggest that tumor resection should be avoided [14]. There are conflicting results about the beneficial effect of cytoreductive surgery in patients with breast cancer. Some studies showed that debulking surgery in patients with breast cancer may be beneficial, especially in patients with late recurrences (5 or more years) [18, 19]. However this beneficial effect has not been shown in other studies [4, 15]. The results of some studies support the role of debulking surgery in the management of tumors of stomach origin [20, 21]. In our study, the primary site and histopathologic subtype of the NGOM were found to be prognostic factors in multivariate analysis. Krukenberg was a poor prognostic factor in accord with the literature. Age, peritoneal carcinomatosis, surgical procedure and cytoreduction were not found to be prognostic factors. Although this study was retrospective, nonrandomized, included a heterogenous patient population, and had a small number of cases for some primary sites of NGOM, no comment can be made for the surgical modalities. This limited retrospective review is noteworthy for the preoperative evaluation of NGOM.

Conclusion

Surgery is frequently indicated for diagnosis of an ovarian mass and also for relief of symptoms in most cases but surgical procedures and especially maximum surgical efforts in patients with NGOM are not yet clear enough. In conclusion, preoperative evaluation methods should carefully be reviewed for these patients to avoid inappropriate procedures and complications.

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