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Preoperative diagnosis of metastatic ovarian cancer is related to origin of primary tumor

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KEYWORDS: CA 125; color Doppler; metastases; metastatic ovarian cancer; ultrasonography

ABSTRACT

Objective *To describe the gray-scale and color Doppler ultrasound features as well as some clinical and biochemical features of metastatic ovarian tumors according to the origin of the primary tumor in a large study population,*

Methods *This was a retrospective analysis of 116 masses in 92 patients (mean age, 51 years) evaluated and treated at three European university centers for a metastatic tumor in the ovary. All patients had undergone transvaginal color Doppler ultrasound according to a standardized protocol prior to surgery and tumor removal. Ultrasound features analyzed were bilaterality, tumor volume, morphologic gray-scale appearance and color score. CA 125 was also recorded.*

Results *Primary tumor histological diagnosis was as follows: colon-sigmoid* (n = *32), stomach* (n = *28), breast* (n = *20), uterus* (n = *17), lymphoma* (n = *4), liver-pancreas-biliary tract* (n = *4) and miscellaneous* (n = *11). There were no differences in age, menopausal status or CA 125 values according to origin of primary tumor. Bilaterality was significantly more frequent in stomach metastases (56%) in comparison with colon-sigmoid and liver-pancreas-biliary tract metastases (18.5% and 0%, respectively,* $P < 0.05$*). Median tumor volume was significantly lower in breast metastases (33.5 mL) compared with other metastases* ($P < 0.05$) *except stomach metastases and metastatic tumors from the miscellaneous group. Ovarian metastases from breast cancers were significantly more frequently solid in comparison to stomach, colorectal and uterine cancer metastases (95.0% vs. 60.8%, 46.8% and 70.6%, respectively,* $P < 0.05$*), and tended to appear moderately or highly vascularized. There were no differences in color score among all groups, although the percentage of masses with abundant color was high (50–82%).*

Conclusions *Ovarian metastases derived from breast cancers tend to be small, solid and vascularized; they seem to be the only ovarian metastases whose primary tumor origin can be suspected by ultrasonography preoperatively. Color score does not seem to help suspect the origin of the primary tumor.* Copyright © 2012 ISUOG. *Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Metastatic ovarian tumors are malignant tumors that metastasize to the ovary from extraovarian primary neoplasms. Metastatic ovarian tumors account for approximately 8% of ovarian neoplasms in women undergoing surgery for an adnexal mass in the United States[1]. Few studies have been performed specifically to compare the different characteristics of metastatic ovarian malignancies. This kind of diagnosis could be important because the prognosis of these tumors depends on the origin of the primary tumor[2–4]. To the best of our knowledge, only one study has specifically evaluated the preoperative ultrasonographic appearance of metastatic ovarian cancer; Testa *et al.*[5] reported sonographic morphology according to the origin of the primary tumor in a series of 67 women with metastatic tumors in their ovaries, dividing the metastases into two groups according to their origin. They found that metastases from the stomach, breast, lymphoma or uterus showed a higher percentage of cases with solid pattern, but were smaller and more vascularized, in comparison with metastases deriving from colon, rectum, appendix or biliary tract.

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The aim of our study was to describe the gray-scale and color Doppler ultrasound features as well as some clinical and biochemical features of metastatic tumors to the ovary in a large study population, evaluating and comparing the different primary sites.

SUBJECTS AND METHODS

This was a European multicenter retrospective study including 116 masses in 92 patients with proven histological diagnosis of a metastatic tumor in the ovary. All women had been evaluated and treated between January 1995 and December 2009 at one of three European university centers: Clinica Universidad de Navarra, Pamplona, Spain ($n = 62$); Ospedale San Giovanni di Dio, Cagliari, Italy ($n = 17$) and Institut Universitari Dexeus, Barcelona, Spain ($n = 13$).

In all cases the ovarian tumor was discovered during pretreatment work-up or during follow-up of extraovarian primary malignancy. This means that no tumor was under oncologic treatment when evaluated.

Menopause was defined as 1 year's absence of menstruation in women aged 40 years or older or in those aged 50 years or older in the case of previous hysterectomy. Women around 50 years old with fewer than 12 months of amenorrhea were considered as premenopausal.

Ultrasound examinations were performed by three of the authors (J.L.A., S.G. and M.A.P.) using several commercially available ultrasound machines throughout the study period. A similar scanning protocol was used in all three centers and has been reported previously[6]. Briefly, first, tumor volume was calculated according to the prolate ellipsoid formula (D1 × D2 × D3 × 0.5233, where D1, D2 and D3 are the three diameters of the tumor; expressed in mL). Gray-scale morphological evaluation of the adnexal mass was performed considering the following parameters: bilaterality, septations, papillary projections or solid areas and echogenicity. According to these parameters, tumors were classified as unilocular cyst, multilocular cyst, unilocular-solid cyst, multilocular-solid cyst or solid cyst[7]. After morphological evaluation, the color Doppler gate was activated to identify vascular color signals within the tumor. The amount of vascularization was assessed according to the color content of the tumor using color or power Doppler and was classified as absent (color score 1), scanty (score 2), moderate (score 3) or abundant (score 4)[6].

On the same day as the ultrasound examination, blood samples were collected for serum CA 125 level determination. An enzymoimmunoassay with monoclonal antibody was used (Cobas-Core CA-125-II™, Laboratories Roche, Basel, Switzerland). Its sensitivity was < 5 U/mL. The inter- and intra-assay coefficients of variation were < 7.5% and < 5.3%, respectively.

All tumors were removed surgically and definitive histological diagnosis was obtained.

Variables were assessed as follows: (1) clinical: patient's age and menopause (yes/no); (2) laboratory: serum CA 125 level expressed in U/mL; (3) ultrasound features: bilaterality (yes/no), B-mode appearance, color score and tumor volume; (4) histological diagnosis. Categorical data are presented as percentage and continuous data as median and range. The Kolmogorov–Smirnov test was used to assess data distribution.

Continuous variables were compared using one-way ANOVA with Bonferroni post-hoc test or Kruskal–Wallis test, depending on data distribution. The chi-square test was used for comparing categorical variables.

As this was a retrospective study and ultrasound examination is performed routinely for assessing adnexal masses in all three centers, institutional review board approval was not necessary.

RESULTS

Twenty-four (26%) patients had bilateral tumors on ultrasound evaluation, so the total number of tumors assessed was 116. The origin of the primary tumor of the 116 ovarian masses is provided in Table 1. The patients' median age was 51.3 (range, 17–82) years. Forty-nine (53.3%) women were postmenopausal and 43 (46.7%) were premenopausal.

There were no differences in age, menopausal status or median CA 125 values (Table 2) according to origin of primary tumor. Bilaterality was most frequent in metastases that derived from the stomach (55.6%) and was never present in lymphoma and liver-pancreas-biliary tract metastases (Table 2). Median tumor volume was significantly lower in breast metastases (33.5 mL) compared with all kinds of metastases except stomach metastases and metastatic tumors from the miscellaneous group (Table 2). Colorectal cancer metastases were significantly larger compared with stomach, breast and metastatic tumors from miscellaneous group.

Seventy-five (64.7%) of the masses included in the study were purely solid, six (5.2%) were unilocular-solid and 35 (30.2%) were multilocular-solid. No mass showed a purely unilocular or multilocular pattern. On B-mode ultrasound, solid tumor appearance was significantly more frequent in breast metastases (95%) (Figure 1) than in stomach, colorectal (Figure 2) and uterine cancer

Table 1 Primary tumor origin of 116 ovarian metastatic tumors

Primary tumor origin	n	%
Colorectum	32	27.6
Stomach	28	24.1
Breast	20	17.2
Uterus*	17	14.7
Lymphatic system	4	3.4
Liver-pancreas-biliary tract†	4	3.4
Miscellaneous‡	11	9.5

*Including 13 endometrial cancers and four leiomyosarcomas. †Including two cholangiocarcinomas, one pancreatic cancer one liver carcinoma. ‡Including four malignant mesothelioma, two carcinoids, two carcinomas of the appendix, one ureteral carcinoma, one lung carcinoma and one melanoma.

Table 2 Clinical, CA 125 and some ultrasound findings in 92 patients with 116 ovarian metastatic tumors according to origin of primary tumor

Primary tumor origin	*Patient age (years)**	*Menopause**	*CA 125 (U/mL)**	*Bilaterality†*	*Tumor volume (mL)‡*
Colorectum	51.0 (31–82)	48.1	83.7 (1.9–930.7)	18.5	234.4 (14.3–2315.3)
Stomach	46.0 (30–67)	44.4	85.8 (5.6–594.0)	55.6	144.9 (11.5–744.5)
Breast	46.0 (38–65)	56.3	80.3 (9.2–2134.0)	25.0	33.5 (9.2–1082.6)
Uterus	57.0 (29–77)	57.1	111.0 (11.4–1068.0)	21.4	119.5 (5.0–659.2)
Lymphatic system	66.5 (41–70)	75.0	154.2 (6.3–809.9)	0	333.0 (225.0–418.6)
Liver-pancreas-biliary tract	51.0 (17–68)	50.0	90.1 (75.0–101.0)	0	175.5 (80.4–635.8)
Miscellaneous	57.0 (36–69)	66.7	47.3 (8.5–5200.0)	22.2	58.2 (10.0–667.0)

Data expressed as median (range) or %. *No differences among groups. †$P < 0.05$ for metastases of stomach cancer vs. colon-sigmoid, lymphoma and liver-pancreas-biliary tract metastases; no differences among all other groups. ‡$P < 0.05$ for metastases of breast cancer vs. colon-sigmoid, uterine, lymphoma and liver-pancreas-biliary tract metastases, for metastases of colon-sigmoid cancer vs. stomach and miscellaneous ovarian metastases and for metastases of stomach cancer vs. lymphoma metastases; no differences among all other groups.

Figure 1 Typical solid appearance on B-mode ultrasound of metastasis from breast carcinoma.

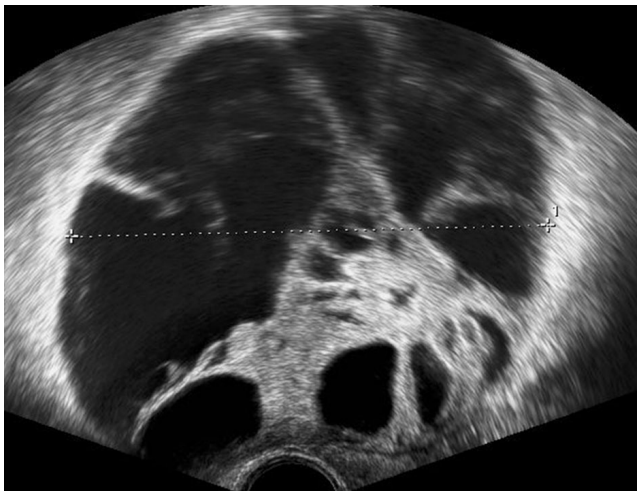

Figure 2 Ovarian metastatic tumor (calipers) deriving from colon carcinoma with a multilocular-solid appearance on B-mode ultrasound.

metastases. No further differences were observed among the groups (Table 3). Most tumors were moderately or highly vascularized (Figures 3 and 4) but there were no differences in color score (Table 4) between metastases of different primary tumor origin.

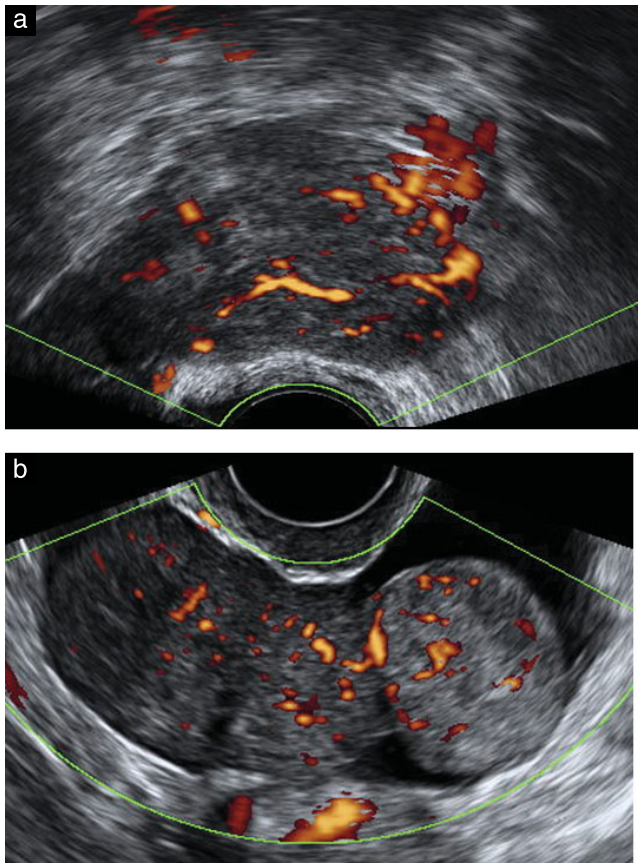

Figure 3 Ovarian metastases from stomach carcinoma (a, highly vascularized) and breast carcinoma (b, moderately vascularized) on color Doppler evaluation.

Although ovarian metastatic tumors showed relatively few specific ultrasonographic findings, with the aim of comparing our data with one of the few previously published studies on this topic[5], we grouped tumors in the same manner as was done by Testa *et al.*, comparing metastases deriving from the stomach, breast, lymphatic system or uterus with metastases deriving from the colon, rectum, appendix or biliary tract. We found that metastases from the stomach, breast, lymphatic system or uterus were purely solid in 75.4% (52/69) of cases while

Table 3 Appearance of 116 ovarian metastatic tumors on B-mode ultrasound according to primary tumor

	Tumor appearance on B-mode ultrasound			
Primary tumor origin	*Unilocular or multilocular*	*Unilocular-solid or multilocular-solid*	*Solid**	*Total*
Colorectum	0	17 (53.2)	15 (46.8)	32
Stomach	0	11 (39.2)	17 (60.8)	28
Breast	0	1 (5.0)	19 (95.0)	20
Uterus	0	5 (29.4)	12 (70.6)	17
Lymphatic system	0	0 (0)	4 (100.0)	4
Liver-pancreas-biliary tract	0	2 (50.0)	2 (50.0)	4
Miscellaneous	0	5 (45.5)	6 (54.5)	11

Data expressed as *n* (%) or *n*. **P* < 0.05 for metastases of breast cancer as compared with stomach, colon-sigmoid and uterine cancer metastases; no differences among all other groups.

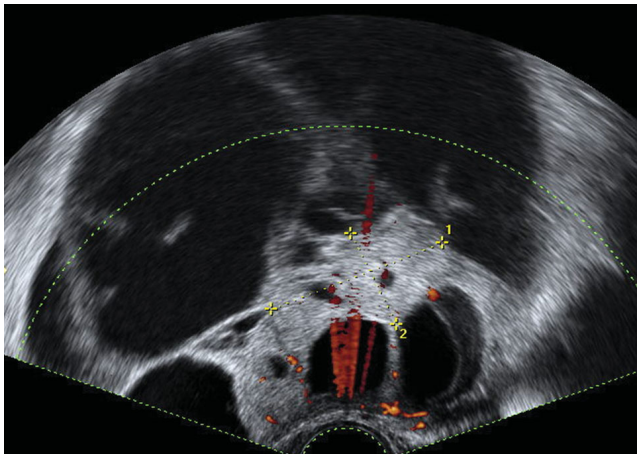

Figure 4 Ovarian metastatic tumor (calipers) deriving from colon carcinoma with scanty vascularization on color Doppler evaluation.

metastases deriving from the colon, rectum or biliary tract were solid in 47% (17/36) of cases ($P = 0.009$). There were no differences between these groups in terms of age or CA 125 value. The median volume of metastases from the stomach, breast, lymphatic system or uterus was significantly smaller than that of metastases deriving from the colon, rectum or biliary tract (65 (range, 5–1082) mL vs. 234 (range, 14–2315) mL, $P = 0.009$). With respect to color score, there was no significant difference between metastases from the stomach, breast, lymphoma or uterus and metastases deriving from the colon, rectum, appendix or biliary tract because of the similar percentage of masses with moderate–abundant color (85% vs 86%, $P = 0.933$).

DISCUSSION

To our knowledge, this is the second published study to specifically investigate the preoperative evaluation of metastatic tumors of the ovary. The relatively large number of cases included in our study (the largest reported in the literature to date) permitted a more accurate analysis of different parameters in each group (e.g. there were more than 30 colorectal metastases), although the retrospective nature of the study is a possible bias. However, we used the same standardized preoperative protocol for all masses and used an accurate description of the mass, avoiding, for example, the confounding term 'complex mass'. In addition, our study investigated some clinical and biochemical parameters, such as CA 125, in all cases. Our study did not find any clinical or biochemical factors suggestive of any one particular type of metastatic tumor; there were no differences in age, menopausal status or CA 125 values among the different metastatic tumors. Thus, it is impossible to identify a typical patient on the basis of menopausal status, age or CA 125 value in which a particular type of metastasis is more frequent.

Some simple ultrasonographic parameters, such as bilaterality and volume, agreed fairly well with descriptions in pathology textbooks of metastatic tumors in the

Table 4 Color score of 116 ovarian metastatic tumors with respect to primary tumor origin

Primary tumor origin	*Absent (Score 1)*	*Scanty (Score 2)*	*Moderate (Score 3)*	*Abundant (Score 4)*	*Total*
Colorectum	0 (0)	4 (12.5)	5 (15.6)	23 (71.9)	32
Stomach	0 (0)	2 (7.1)	3 (10.7)	23 (82.1)	28
Breast	2 (10)	0 (0)	5 (25.0)	13 (65.0)	20
Uterus	0 (0)	5 (29.45)	3 (17.6)	9 (52.9)	17
Lymphatic system	0 (0)	1 (25.0)	1 (25.0)	2 (50.0)	4
Liver-pancreas-biliary tract	0 (0)	0 (0)	1 (25.0)	3 (75.0)	4
Miscellaneous	1 (9.1)	2 (18.2)	1 (9.1)	7 (8.8)	11

Data expressed as *n* (%) or *n*.

ovaries[1,8]. Bilaterality was significantly more frequent in stomach vs. colon-sigmoid and liver-pancreas-biliary tract metastases. As previously reported by Testa *et al.*[5], we also found a rate of bilaterality lower than that reported in pathology textbooks and articles[1,8–10].

Median tumor volume was significantly lower in breast metastases compared with colorectal, uterine, lymphatic system and liver-pancreas-biliary tract metastases, while metastases of colon-sigmoid cancer were considerably larger than stomach metastases. These observations are in agreement with the findings of Testa *et al.*[5].

Regarding B-mode appearance, all metastatic tumors included in this study were solid, multilocular solid or at least unilocular solid. There were no cases of purely unilocular or multilocular masses. Ovarian metastases derived from breast tumors were particularly small and solid and seem to be the only type that may be suspected by ultrasonography preoperatively. This could be of value when following up the many patients with breast cancer. One finding was that these tumors are moderately or highly vascularized. We consider this finding important for differentiating breast metastases from other solid benign ovarian tumors, such as ovarian fibromas, which tend to appear avascular or with scanty vascularization. Our study therefore suggests that the diagnosis of a unilocular cyst in a follow-up pelvic scan should not raise suspicion of metastatic disease, while visualization of a small solid tumor should lead the clinician to perform mammography in order to exclude the presence of a primary breast carcinoma.

In agreement with the findings of Testa *et al.*[5], a purely solid pattern was found in only 50% of 30 malignancies derived from colorectal cancer. According to pathology textbooks, also from a preoperative point of view, ovarian metastases from primary gastrointestinal malignancies differ on the basis of their origin (stomach or colorectum) although in several papers these origins are considered together[9,10]. Usually, colorectal metastases are difficult to differentiate from primary ovarian cancer, both by ultrasound and microscopically. On ultrasound, these metastatic tumors are usually large and have a considerable cystic component.

Testa *et al.*[5], in their report of sonographic morphology according to the origin of the primary tumor, in a series of 67 women with metastatic tumors in their ovaries, arbitrarily grouped the tumors into two groups, one including metastatic tumor from stomach, breast, lymphatic system and uterus and one including tumors from colon, rectum, appendix or biliary tract. They found that metastases in the first group are solid while those in the second are multilocular or multilocular-solid. We partially confirmed these data in our larger population, although we found no purely multilocular masses. In comparison with the findings of Testa *et al.*[5], the metastases derived from stomach cancer in our study were less frequently solid than expected. Our data are confirmed by pathologists who found a cystic component in one third of such tumors[11]; we found a cystic component in 39% of cases. Our study in a large population confirms that, as reported by Testa *et al.*[5], metastases deriving from lymphoma and breast cancers show a solid appearance in almost all cases, and the overall rate of completely solid masses is comparable between the two studies. Both studies also showed some additional similarities. Although not originally claimed by Testa *et al.*, the overall rate of solid tumors calculated from the raw data they reported seems similar to ours (65% and 66%, respectively) and these rates are lower than those reported in studies comparing primary and metastatic tumors[12–14]. Using the approach of Testa *et al.*[5] of pooling some groups of tumor together, we confirm that dimensions and B-mode findings (solid appearance) of metastases from the stomach, breast, lymphatic system or uterus are significantly different from those of metastases deriving from colon, rectum or biliary tract tumors.

Our findings regarding the role of color Doppler differ from those of Testa *et al.*[5]; we did not find color score to be useful in determining the origin of the primary tumor, and we found no difference using their grouping of metastases from stomach, breast, lymphatic system or uterus vs those from colon, rectum or biliary tract, both groups having a similar percentage of masses with moderate–abundant color. The difference between the two studies could be due to the higher number of cases of colorectal metastases in our study. Testa *et al.*[5] found a color score of 3–4 in 70% of malignancies derived from the colorectum.

In conclusion, despite the absence of differences between some kinds of metastases, from a practical point of view we found that most (75/116) metastatic tumors were solid, fewer than expected were bilateral, and no metastatic tumor had purely unilocular or multilocular morphology. In addition, the majority of tumors had clinical characteristics highly suggestive of malignancy: 70% of all tumors were solid, the mean CA 125 values were significantly elevated, and most women were postmenopausal. As such, the majority of clinicians would agree that surgical removal is warranted, regardless of primary tumor origin.

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