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Imaging in gynecological disease (1): ultrasound features of metastases in the ovaries differ depending on the origin of the primary tumor

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KEYWORDS: metastatic; ovarian neoplasms; ultrasonography

ABSTRACT

Objective *To describe the gray-scale and color Doppler ultrasound findings of metastatic tumors in the ovary according to the origin of the primary tumor.*

Methods *Information was retrieved retrospectively from 67 patients who had undergone preoperative transvaginal gray-scale and color Doppler ultrasound examination and who were found subsequently to have metastatic tumors in their ovaries. In all women the ultrasound information had been collected prospectively using a standardized examination technique and predefined definitions of ultrasound characteristics. Stored ultrasound images were used only to describe retrospectively the external surface of the metastatic tumors. Information on presenting symptoms and on whether the patient had been treated for a malignancy in the past was retrieved retrospectively from patient records.*

Results *Most (95%) ovarian metastases were solid, multilocular-solid or multilocular. Almost all (38/41, 93%) metastases that derived from the stomach, breast, lymphoma or uterus were solid, while most (16/22, 73%) metastases deriving from the colon, rectum, appendix or biliary tract were multilocular or multilocular-solid ($P < 0.0001$). Metastases that derived from the colon, rectum, appendix or biliary tract were larger compared with those from the stomach, breast, lymphoma or uterus (median maximum diameter, 122 (range, 16–200) mm vs. 71 (range, 27–170) mm, $P = 0.02$). In addition, irregular external borders were more common (19/22 (86%) vs. 19/41 (46%), $P = 0.002$), as were papillary projections (6/22 (27%) vs. 2/41 (5%), $P = 0.011$). They also appeared to be less vascularized, with 64% (14/22) manifesting moderate-to-abundant vascularization at color Doppler examination in comparison to 88% (36/41) of the ovarian metastases from stomach, breast, lymphoma or uterus ($P = 0.024$).*

Conclusion *Ovarian metastases derived from lymphoma or from tumors in the stomach, breast and uterus are solid in almost all cases, whereas those derived from the colon, rectum or biliary tract manifest more heterogeneous morphological patterns, most being multicystic with irregular borders. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Aim

To describe the gray-scale and color Doppler ultrasound findings of metastatic tumors in the ovaries according to the origin of the primary tumor.

Background

Epidemiology

The ovary is a common site of metastases from malignant tumors, 5–20% of ovarian masses being metastases from primary tumors in other organs[1–3]. Most (50–90%) metastases in the ovaries originate from the gastrointestinal tract or the breast[4].

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Macroscopic appearance

Pathological reports describe metastatic tumors as often (about 60% of cases) being bilateral lesions that appear as diffusely solid tumors, multiple solid nodules, partly cystic masses or, rather uncommonly, entirely cystic lesions[2]. Even when the primary tumor is solid, metastases in the ovaries may be cystic or semicystic. Extensive areas of hemorrhage and/or necrosis are common[2]. Krukenberg tumors are typically solid masses with a bosselated outer surface.

Microscopic appearance

Microscopically, metastatic tumors show a variety of patterns, depending on the site of the primary tumor. Features indicative of a metastatic tumor include extensive areas of necrosis, surface implants, a multifocal pattern and vascular invasion[5].

Krukenberg tumors are traditionally defined as being composed of mucin-filled signet-ring cells associated with a striking proliferation of cellular non-neoplastic ovarian stroma. The typical microscopic pattern is a juxtaposition of compact areas containing tumor cells, stromal elements and pale edematous zones[6]. In Krukenberg tumors, the most common primary tumors are those of the stomach, large intestine, appendix and breast[7].

Clinical symptoms

The symptoms of metastatic tumors in the ovaries are non-specific and related to the presence of a pelvic mass. Sometimes patients are asymptomatic and diagnosed at a routine follow-up examination. An ovarian mass may be the initial manifestation of a primary tumor located elsewhere, the primary tumor being detected only following the diagnosis of the metastatic tumor[4]. In Krukenberg tumors, although the symptoms are usually unspecific, endocrine manifestations, such as virilization during pregnancy, may result from stromal luteinization[7].

Prognosis

The prognosis for patients with a metastatic tumor in the ovary is poor, with a 5-year survival period in 36% of cases and a median survival of 42 months[3]. Survival time depends on the origin of the primary tumor; the median survival time for ovarian metastases from breast cancer is 36–54 months, that from colorectal cancer is 48 months and that from lymphoma is 181 months[3,8]. The prognosis for a woman with a Krukenberg tumor is extremely poor, with a 5-year survival period in 12% of cases[9].

METHODS

The study included 67 patients. Of these, 23 were included in the International Ovarian Tumor Analysis (IOTA) study[10] and 44 came from a consecutive series of 774 women with at least one adnexal mass, who were examined after completion of the first phase of the IOTA study but using the IOTA study protocol. This series of 44 patients included patients from the Gynecology Oncology Unit, University of Sacred Heart, Rome (Italy), the Department of Obstetrics and Gynecology, Katholieke Universiteit Leuven (Belgium), the Department of Obstetrics and Gynecology, Malmö University Hospital, Malmö (Sweden) and the Department of Obstetrics and Gynecology, University of Bologna (Italy). All diagnoses were made on the basis of histopathological examination of excised specimens. Only women with a metastatic tumor in the ovary were included. Women with recurrent ovarian cancer and ovarian involvement from serous papillary carcinoma of the peritoneum were excluded. Of the 42 patients defined as having metastatic tumors in the IOTA database[10], we excluded 19 (because of undefined primary tumor ($n = 9$), pelvic metastatic mass but normal ovaries ($n = 2$), recurrent ovarian cancer ($n = 3$), serous papillary peritoneal cancer ($n = 3$) or neuroendocrine tumors ($n = 2$)).

All women underwent preoperative transvaginal gray-scale and color Doppler ultrasound examination using high-end ultrasound equipment, a standardized examination technique and standardized terms and definitions, which have been described in a previous publication[11]. A transabdominal ultrasound examination was also performed if necessary. Briefly, ovarian lesions were classified as unilocular, unilocular-solid, multilocular, multilocular-solid or solid. Standardized color Doppler settings were used, and a subjective semiquantitative assessment of the amount of detectable blood flow within each tumor was made using a color score. A color score of 1 was given when no color could be detected in the lesion, a score of 2 was given when only minimal color could be detected, a score of 3 was given when a moderate amount of color was present and a score of 4 was given when the tumor appeared highly vascularized[11]. When color Doppler signals were detected, the ultrasound examiner tried to identify the tumoral artery with the highest blood flow velocity. For this purpose the color Doppler sensitivity was reduced by increasing the pulse repetition frequency until only one vessel was detectable. Pulsed Doppler examination of this vessel enabled spectral analysis of the blood flow. The pulsatility index, the resistance index, the peak systolic velocity and the time-averaged maximum velocity were recorded.

Ultrasound images were stored on a hard disk. Stored images were used to describe retrospectively the external surface of the metastatic tumors. Information on presenting symptoms and on whether or not the patient had been treated for a malignancy previously was retrieved retrospectively from patient records. All other ultrasound information and some clinical information were collected prospectively as described in previous publications[10,12]. Serum levels of CA 125 were measured using the CA 125 II immunoradiometric assay (Centocor, Malvern, PA, USA or Abbott Axsym system, REF 3B41-22, Abbott Laboratories Diagnostic Division, IL, USA), but information on CA 125 was not a prerequisite for inclusion in the study.

Statistical analysis

If histopathology confirmed that both ovaries harbored metastatic disease, the mass with the worst sonographic appearance, or the largest mass if the sonographic appearances were similar, was selected for statistical analysis. Univariate analysis was performed using Fisher's exact test for categorical data and the Mann–Whitney test for numerical data. Two-sided tests were used with 5% as the level of significance (α-level = 0.05). Statistical analysis was performed using the SPSS 9.0 statistical package (SPSS Inc, Chicago, IL, USA).

RESULTS

The origin of the primary tumors was colon–rectum in 14 cases (21%), appendix in three cases (5%) (two mucinous tumors, one carcinoid), stomach in 15 cases (22%), uterus in 13 cases (19%) (two leiomyosarcomas, one endometrial stromal sarcoma, eight endometrial carcinomas, one tubal cancer, one cervical cancer), breast in ten cases (15%), biliary tract in five cases (7%), pancreas in four cases (6%) and lymphoma in three cases (5%). In all three cases of lymphoma the ovarian involvement was a result of the spread of generalized disease. In all Krukenberg tumors the primary tumor was stomach cancer.

In 29 (43%) of the 67 patients, the ovarian mass was detected at a planned follow-up visit because of a previous diagnosis of a malignancy, and 17 (59%) of these patients were asymptomatic. In the other 38 (57%) patients, the pelvic mass was detected before the primary tumor was diagnosed, and 21 (55%) of these patients were symptomatic (bloating in 16 patients and pelvic pain in five patients). The median age at diagnosis was 56 (range, 25–82) years and the age was similar for all types of primary tumor, with the exception that the three patients with primary malignancy of the appendix were younger (25, 30 and 48 years old). The CA 125 level was available in 43 patients, and 33 (77%) had a value > 35 U/mL (median, 87; range, 14–1648).

Table 1 Sonographic characteristics of metastatic tumors in the ovaries in a series of 67 women

Characteristic	n *(%) or median (range)*
Diameter (mm)	89 (16–220)
Locularity	
Unilocular	1 (1.5)
Unilocular-solid	2 (3.0)
Multilocular	8 (12.0)
Multilocular-solid	12 (18.0)
Solid	44 (65.5)
Irregular margins	42 (63.0)
Echogenicity	
Anechoic	12 (18.0)
Low level	13 (19.5)
Ground glass	1 (1.5)
Hemorrhagic	1 (1.5)
Mixed	5 (7.5)
No cystic fluid	35 (52.0)
Papillary projections	8 (12.0)
Color score	
1	3 (4.0)
2	12 (18.0)
3	28 (42.0)
4	24 (36.0)
Pulsatility index	0.62 (0.36–2.42)
Resistance index	0.46 (0.2–0.95)
Peak systolic velocity (cm/s)	22 (6–80)
Time-averaged maximum velocity (cm/s)	16 (3–47)

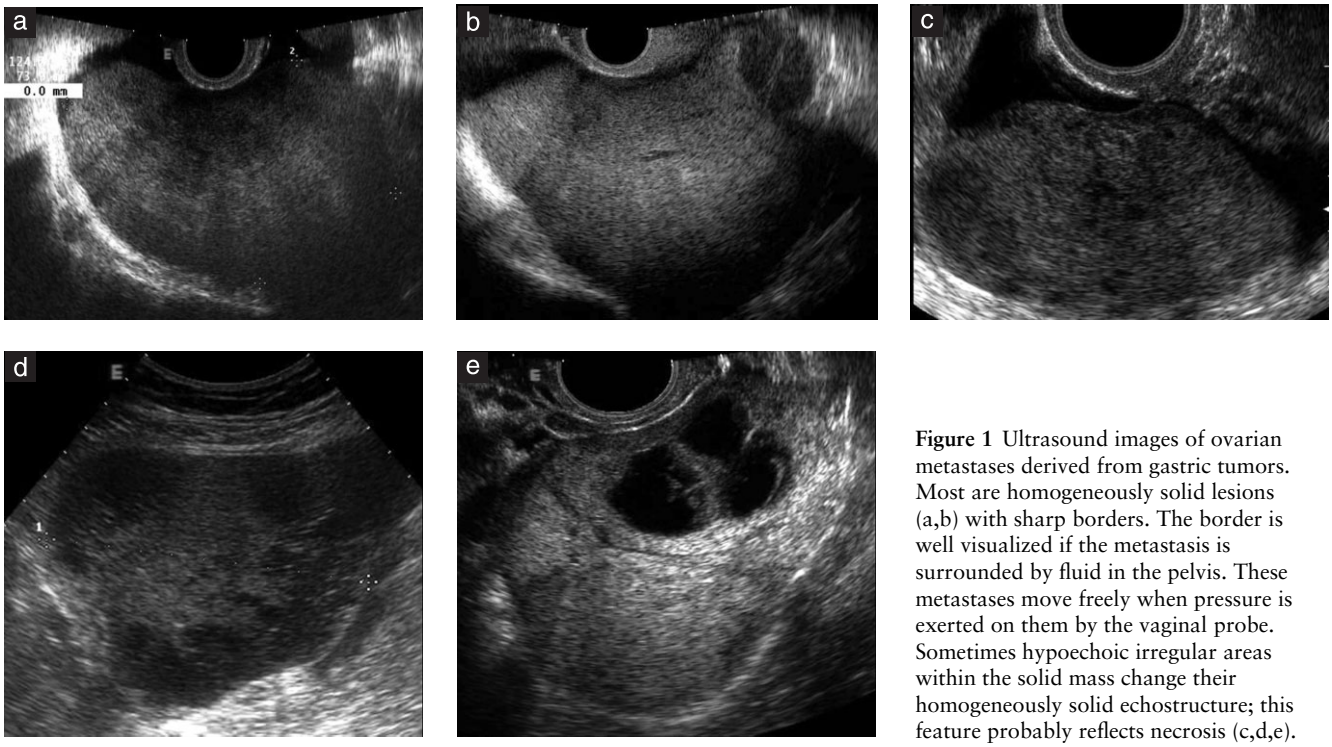


Figure 1 Ultrasound images of ovarian metastases derived from gastric tumors. Most are homogeneously solid lesions (a,b) with sharp borders. The border is well visualized if the metastasis is surrounded by fluid in the pelvis. These metastases move freely when pressure is exerted on them by the vaginal probe. Sometimes hypoechoic irregular areas within the solid mass change their homogeneously solid echostructure; this feature probably reflects necrosis (c,d,e).

Table 2 Sonographic morphology according to the origin of the primary tumor in a series of 67 women with metastatic tumors in their ovaries

	Origin of primary tumor						
	Colon/ rectum/ appendix	*Biliary tract*	*Stomach*	*Lymphoma*	*Breast*	*Uterus*	*Pancreas*
Number of patients	17	5	15	3	10	13	4
Locularity (*n* (%))							
Unilocular	1 (5.5)	—	—	—	—	—	—
Unilocular-solid	1 (5.5)	—	—	—	—	—	1 (25)
Multilocular	4 (24)	3 (60)	—	—	1	—	—
Multilocular-solid	8 (47)	1 (20)	—	—	—	2 (15)	1 (25)
Solid	3 (18)	1 (20)	15 (100)	3 (100)	9 (90)	11 (85)	2 (50)
Diameter (mm, median (range))	113 (16–179)	150 (55–200)	84 (43–170)	120 (73–130)	55 (27–98)	82 (28–220)	89 (44–149)
Irregular borders (*n* (%))	15 (88)	4 (80)	7 (47)	1 (33)	5 (50)	6 (46)	4 (100)
Echogenicity (*n* (%))							
Anechoic	4 (24)	1 (20)	2 (13)	—	1(10)	2 (15)	2 (50)
Low level	8 (47)	3 (60)	1 (7)	—	—	1 (8)	—
Ground glass	—	—	—	—	—	1 (8)	—
Hemorrhagic	1 (6)	—	—	—	—	—	—
Mixed	2 (11.5)	—	—	—	—	2 (15)	1 (25)
No cystic fluid	2 (11.5)	1 (20)	12 (80)	3 (100)	9 (90)	7 (54)	1 (25)
Papillary projections (*n* (%))	6 (35)	0	0	0	0	2 (15)	0
Color score (*n* (%))							
1	1 (6)	—	—	—	—	—	2 (50)
2	4 (24)	3 (60)	2 (13)	—	2 (20)	1 (8)	—
3	7 (41)	2 (40)	8 (54)	—	4 (40)	6 (46)	1 (25)
4	5 (29)	—	5 (33)	3 (100)	4 (43)	6 (46)	1 (25)

Table S1 online shows these data with confidence intervals.

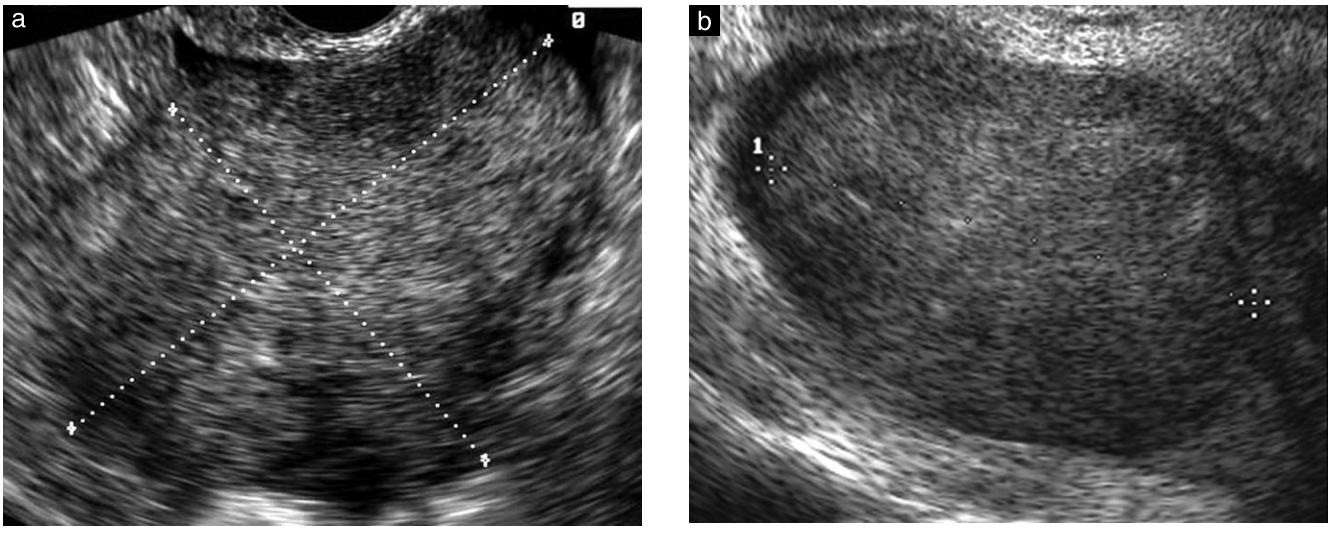
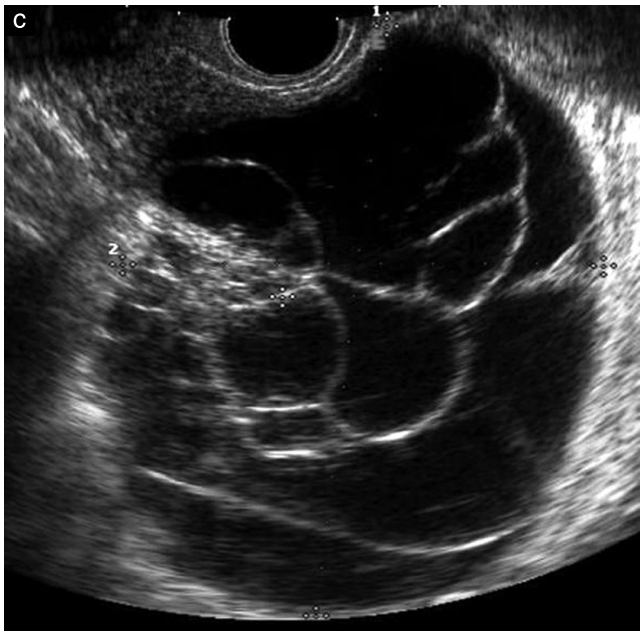


Figure 2 Ovarian metastases derived from breast cancer (a) and from lymphatic malignant disease (b) manifest ultrasound morphology similar to that of metastases derived from gastric tumors (see Figure 1).

The ovarian masses were associated with the presence of ascites in 39% of cases. At surgery, 36 (54%) patients were found to have bilateral ovarian lesions. Sonography correctly detected bilateral lesions in 26 (72%) of these cases, and in these cases the ultrasound morphology was similar (e.g. solid or multilocular solid) in both tumors in 22 (85%) cases.

The sonographic characteristics of the metastatic ovarian tumors are shown in Table 1. Most (95%) ovarian metastases were solid, multilocular-solid or multilocular. Most of the multilocular and multilocular-solid tumors (16/20, 80%) contained more than ten locules. In terms of echogenicity, the cystic fluid was anechoic or of low echogenicity in 78% (25/32) of cases. Papillary projections



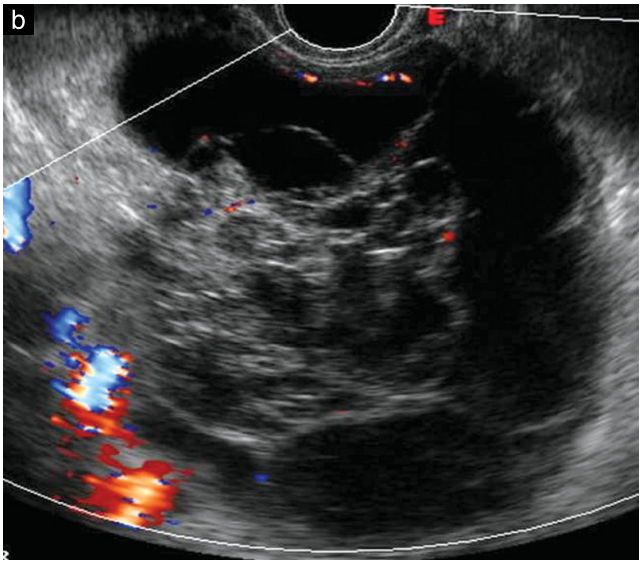


Figure 3 Ultrasound images of ovarian metastases derived from the large intestine and biliary tract. A typical feature is multilocularity with a very large number of locules (a,b,c). The outer surface appears irregular (a,b,c) without a recognizable capsula delineating the lesion (a). Intracystic septa may appear fragmented, possibly because of necrosis (b). In some cases (c) septa are so close to each other that it may be difficult to determine sonographically whether there is a solid part.

were detected in eight (12%) patients and more than three papillary projections were seen in seven of these eight cases. Most metastases were vascularized moderately or richly, exhibiting a color score of 3 or 4 in 78% (52/67) of cases.

Table 2 describes the sonographic morphology of the metastatic tumors according to the origin of the primary tumor. Almost all metastases that were derived from stomach, breast, lymphoma or uterus (38/41, 93%) were solid. Figures 1 and 2 show representative ultrasound images of ovarian metastases from stomach and breast cancers with their typical solid pattern. A solid pattern was found in only four (18%) of 22 malignancies derived from colon, rectum, appendix or biliary tract ($P < 0.0001$). Instead, metastases from the colon, rectum, appendix or biliary tract were most often multilocular or multilocular-solid. Figure 3 shows representative ultrasound images of ovarian metastases from colon cancer with a multilocular pattern. Metastases in the ovaries that were derived from the colon, rectum, appendix or biliary tract were larger than were those derived from the stomach, breast, lymphoma or uterus (median maximum diameter, 122 (range, 16–200) mm vs. 71 (range, 27–170) mm, $P = 0.02$). Also, in these metastases, irregular external borders were more common (19/22 (86%) vs. 19/41 (46%), $P = 0.002$), as were papillary projections (6/22 (27%) vs. 2/41 (5%), $P = 0.011$). They also appeared to be less vascularized, with 64% (14/22) manifesting a color score 3 or 4 on color Doppler examination in comparison to 88% (36/41) of the ovarian metastases from stomach, breast, lymphoma or uterus ($P = 0.024$) (Figure 4). The spectral Doppler results did not differ between the two groups of tumors.

All four ovarian metastases from pancreatic cancer had irregular outer borders, but their sonographic morphology varied: one was a unilocular-solid lesion, one was a multilocular-solid lesion and two were solid masses.

DISCUSSION

We have described here the sonographic patterns of metastases in the ovaries and we have analyzed their morphological features according to the origin of the primary tumor. Our results show that ovarian metastases derived from stomach cancer, breast cancer, lymphomas and uterine cancer are solid in almost all cases, whereas those derived from the colon, rectum and biliary tract manifest more heterogeneous morphological patterns, most being cystic with many cyst locules and irregular borders. Papillary projections seem to be relatively rare (12%) in metastatic tumors in the ovaries. Our results agree with those of Choi *et al.*[13], who noted that

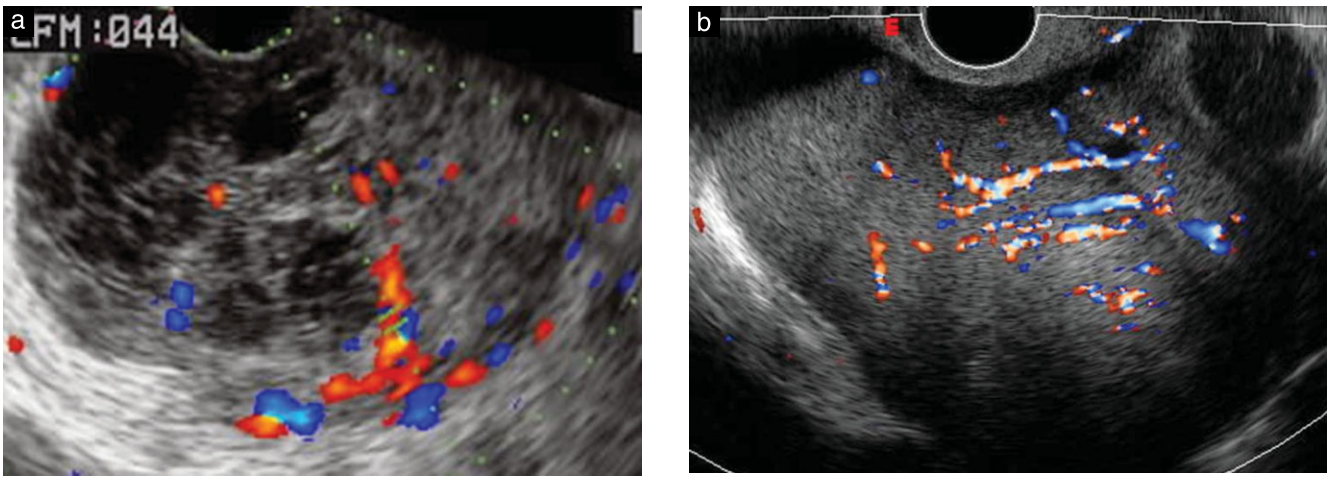


Figure 4 Color Doppler ultrasound images of (a) an ovarian metastasis derived from colon cancer with vessels within the septa (color score 2) and (b) an ovarian metastasis derived from gastric cancer (color score 3).

ovarian metastases from colorectal cancer were cystic on computed tomography, while those derived from stomach cancer appeared to be mostly solid. Our results also agree fairly well with descriptions made of metastatic tumors in the ovaries in pathology textbooks[7–14], except that bilaterality was slightly less common in our series (54% vs. the reported 67–75%). According to pathology textbooks, most ovarian metastases originating from stomach, breast or lymphoma are solid, whereas most ovarian metastases originating from the large intestine are cystic. In the small series of seven cases of ovarian metastases from the biliary tract described in Blaustein's textbook of pathology[7], five were solid, whereas in our small series, four of five were predominantly cystic; in the small series of seven ovarian metastases from tumors in the pancreas described in Blaustein's textbook, most were large, cystic and multiloculated, whereas in our small series of four cases, two were solid. These slightly discrepant results may be explained by the series compared being small, the small series in turn being explained by the rarity of these types of tumor. Our results also agree with those reported in pathology textbooks[7–14] that the cystic fluid in ovarian metastases from the colon is usually serous or mucinous (anechoic or low-level echogenicity of cystic fluid) and that ovarian metastases from the colon are often large. It is possible that mucin production explains the large tumoral diameter and cystic pattern in ovarian metastases from colorectal cancer. In our series, most metastases appeared to be well vascularized on color or power Doppler ultrasound examination, but metasases from the colon–rectum, appendix and pancreas appeared slighlty less vascularized than did the other metastases.

Discrimination between primary ovarian cancer and metastatic tumors in the ovary is important clinically, because their management is different. Surgical cytoreduction is of the utmost importance in the treatment of primary ovarian cancer, while the impact of surgery on the clinical outcome of metastatic tumors in the ovaries is controversial[15]. Some have suggested that surgical removal of ovarian metastases from colorectal cancer is associated with a favorable outcome[3]. It has also been suggested that surgical removal of pelvic metastases derived from breast cancer improves survival, provided that the metastases are detected more than 5 years after the primary tumor was diagnosed and provided that the metastases can be removed completely[8]. Preferably, a correct diagnosis of primary ovarian cancer vs. ovarian metastases should be made before surgery. However, the correct preoperative diagnosis of metastases in the ovary is a challenge[16]. Differences in sonographic findings between primary ovarian malignancies and metastases in the ovaries have been described in several studies, but in these studies the origin of the primary tumor was not taken into account. In all these studies, metastases in the ovaries were predominantly or purely solid[4,16–21], and in one of the studies they never appeared as unilocular or multilocular cysts[16]. Brown *et al.*[16] demonstrated that multilocularity on sonography or magnetic resonance imaging, but no other features, favored a diagnosis of primary ovarian malignancy over metastasis in the ovary. All these results are at variance with ours. The discrepancies may be explained, at least partly, by differences in the origin of the primary tumors.

It is important to realize that symptoms or clinical findings that can be explained by metastases in the ovaries may be the first signs of a primary tumor in another organ[7]. In cases in which ovarian metastases are suspected clinically, a knowledge of the sonographic characteristics of metastases from primary tumors of different origins (cystic metastases deriving from tumors in the colon–rectum; solid metastases deriving from tumors in the breast and stomach) could facilitate location of the primary tumor.

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SUPPLEMENTARY MATERIAL ON THE INTERNET

The following material is available from the Journal homepage: http://www.interscience.wiley.com/jpages/0960-7692/suppmat (restricted access)

Table S1 Sonographic morphology according to the origin of the primary tumor, showing CIs, in a series of 67 women with metastatic tumors in their ovaries

