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Role of CA125/CEA ratio and ultrasound parameters in identifying metastases to the ovaries in patients with multilocular and multilocular-solid ovarian masses

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KEYWORDS: CA125; CEA; ovary; metastasis; ultrasonography

ABSTRACT

Objectives *To investigate ultrasound features and the best cut-off value of the cancer antigen 125/carcinoembryonic antigen (CA125/CEA) ratio to discriminate ovarian metastases from benign and primary malignant ovarian neoplasms in two selected groups of morphological ovarian masses, namely multilocular masses with five or more locules and multilocular-solid masses.*

Methods *Patients with multilocular (five or more locules) or multilocular-solid ovarian masses, operated on within 3 months of ultrasound examination, and with tumor markers (CEA and CA125) available at diagnosis, were identified retrospectively from three ultrasound centers. The masses were described using the International Ovarian Tumor Analysis (IOTA) terminology. Ultrasound and clinical characteristics were compared between those with an ovarian neoplasm (including benign and primary malignant neoplasms) and those with an ovarian metastasis. Receiver–operating characteristics curve (ROC) analysis was used to evaluate the ability of CA125, CEA and CA125/CEA to differentiate between ovarian neoplasms and ovarian metastases, and their predictive performance was assessed.*

Results *In total, 350 (88.4%) patients with an ovarian neoplasm (including 99 benign, 43 borderline and 197 primary epithelial ovarian carcinomas, seven malignant rare tumors and four other types of invasive ovarian tumor) and 46 (11.6%) patients with an ovarian metastasis were analyzed. On ultrasound examination, ovarian neoplasms were smaller than ovarian metastases (median largest diameter, 97 (range, 20–387) mm* vs *146 (range, 43–259) mm, respectively;* $P < 0.0001$*) and presented with a lower number of cysts with > 10 locules (18.9%* vs *54.3%;* $P < 0.0001$*). ROC curve analysis showed that the best cut-off value of CEA for distinguishing between ovarian neoplasms and ovarian metastases was 2.33 ng/mL. The predictive performance of this CEA cut-off value was: area under the curve (AUC), 0.791 (95% CI, 0.711–0.870); accuracy, 73.7%; sensitivity, 73.1%; specificity, 78.3%; positive predictive value (PPV), 96.2%; and negative predictive value (NPV), 27.7%. The best cut-off value of CA125/CEA for distinguishing between ovarian neoplasms and ovarian metastases was 11.92. The predictive performance of this CA125/CEA cut-off value was: AUC, 0.758 (95% CI, 0.683–0.833); accuracy, 79.8%; sensitivity, 82.3%; specificity, 60.9%; PPV, 94.1%; and NPV, 31.1%.*

Conclusions *CA125/CEA ratio and CEA alone did not show any significant difference in their ability to distinguish between ovarian neoplasms (including benign and malignant) and ovarian metastases in masses with multilocular and those with multilocular-solid morphology. Therefore, in this morphological subgroup of ovarian masses, CEA alone is sufficient to differentiate between ovarian neoplasms and ovarian metastases.*

INTRODUCTION

The ovary is a common site of metastases from malignant tumors, with 5–20% of ovarian masses being metastases from primary tumors in other organs[1–3]. Metastases to the

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ovaries occur more often by hematogenous spread than by extension per continuitatem[4,5]. Their development is predominantly metachronous (after the diagnosis of the primary tumor) rather than synchronous, with a disease-free interval of about 3 years[5].

Ovarian metastases from breast or gastric cancer or lymphoma are typically described on ultrasound examination as solid masses[6–8], and show characteristic 'lead vessels' inside the mass on color Doppler examination[9]. On the contrary, ovarian metastases from the colon-rectum, upper gastrointestinal tract or appendix are described more frequently as multilocular[6,10] or multilocular-solid[5–8].

Whether an ovarian metastasis has multilocular or multilocular-solid morphology depends on the proportion of mucinous epithelium, which determines if it is multilocular, and associated desmoplastic stroma, which determines if it is multilocular-solid. These morphological features make preoperative diagnosis of ovarian metastases difficult, as multilocular and multilocular-solid morphologies are also typical of a variety of benign and primary malignant ovarian neoplasms, such as serous or mucinous cystadenomas, cystadenofibromas, mucinous intestinal-type borderline ovarian tumors and invasive ovarian malignancies[11–13]. Indeed, the preoperative recognition of a potential extragenital origin of an ovarian mass is clinically relevant as it may change significantly the management of the patient and allow for early initiation of appropriate treatment of the primary malignancy.

Overall, multilocular and multilocular-solid masses have been described as difficult to classify on ultrasound examination[14], even in the hands of experienced examiners. The risk of malignancy in multilocular and multilocular-solid masses is related to the number of locules, the diameter of the lesion and the diameter of the solid component (which ranges between 10% and 43%)[15].

Different tumor markers, such as cancer antigen 125 (CA125) and carcinoembryonic antigen (CEA), alone or in combination, have been tested in an attempt to improve preoperative evaluation procedures for differentiating between primary malignant ovarian neoplasms and ovarian metastases[16–18]. To achieve this goal, previous studies have focused on the role of the CA125/CEA ratio. In particular, a cut-off value of 25 has demonstrated high accuracy[16,17], and thus it has been used in clinical practice[19].

The aim of the present study was to investigate ultrasound features and the best cut-off value of the CA125/CEA ratio to differentiate between ovarian neoplasms (including both benign and primary malignant ovarian neoplasms) and ovarian metastases in two select groups of morphological ovarian masses, i.e. multilocular masses with five or more locules and multilocular-solid masses.

METHODS

Between 2002 and 2017, preoperative ultrasound features and the CA125/CEA ratio were analyzed retrospectively in patients with multilocular (five or more locules) or multilocular-solid ovarian masses, including benign and primary malignant ovarian neoplasms and ovarian metastases, examined at three ultrasound centers (Policlinico Gemelli, Catholic University of the Sacred Heart, Rome, Italy; European Institute of Oncology, Milan, Italy; and First Faculty of Medicine, Charles University, Prague, Czech Republic). A total of 396 patients were identified (195 from Milan, 143 from Rome and 58 from Prague). All patients were operated on within 3 months from the ultrasound examination, and both CA125 and CEA values were known at the time of the preoperative examination.

Three hundred and fifty-five (89.6%) of the recruited patients had been included in the International Ovarian Tumor Analysis (IOTA) studies (IOTA Phases 2, 3 and 5)[20,21] and had therefore been investigated using a standardized examination technique following a strict research protocol, with predefined clinical and ultrasound information being collected prospectively. The remaining 41 (10.4%) patients (one from Milan and 40 from Prague) were identified from the databases of the participating ultrasound centers.

Ultrasound examination was performed in a standardized manner using IOTA terminology. For women included in the IOTA studies, all ultrasound data and some clinical information that were included in IOTA protocols were obtained from ultrasound databases. Clinical information not included in the IOTA protocols was collected retrospectively from patient records. For women who had been examined outside the IOTA studies, all clinical and ultrasound parameters were retrieved retrospectively from patient records by a single operator from each center and entered into an Excel file.

All ultrasound examiners had more than 10 years' experience in gynecological ultrasound. Transvaginal and transabdominal examinations were performed for each patient to ensure complete evaluation of the entire abdominal cavity. All ultrasound examinations were carried out using high-end ultrasound equipment. The frequency of the vaginal probes was 5.0–9.0 MHz and that of the abdominal probes was 3.5–5.0 MHz.

In cases of bilateral ovarian masses, the mass with the most complex ultrasound morphology was considered in the analysis. If both masses had similar ultrasound morphology, the largest one was included.

The masses were described using the terms and definitions published by the IOTA group[22], including size and characteristics of the mass. Solid papillary projections were defined as any solid projections into the cystic cavity arising from the cyst wall or from a septum with a height $\geq$ 3 mm. The largest solid component other than a papillary projection was also measured. In some cases, a solid papillary projection was the largest solid component. If this was the case, the papillary projection was recorded and measured both as a papillary projection and as the largest solid component of the mass. The presence of ascites and fluid in the pouch of Douglas was also reported.

Ovarian masses were also assessed on color Doppler examination and scored as follows: no detectable blood flow (color score = 1), minimal blood flow (color score = 2), moderate blood flow (color score = 3) or highly vascular (color score = 4).

The specific diagnosis suggested by the ultrasound examiner in the original ultrasound report was also reported. The gold standard was histological diagnosis of the surgically removed ovarian mass.

Data on histology and origin of tumors in patients with ovarian metastases, presence of synchronous or metachronous metastatic tumors, type of diagnosis (surgery or tru-cut biopsy) and the disease-free interval (time between tumor diagnosis and formation of ovarian metastasis), in case of a metachronous tumor, were collected.

Statistical analysis

According to histological findings, the recruited patients were grouped into two cohorts for comparison: those with an ovarian neoplasm (including both benign and primary malignant ovarian neoplasms) and those with an ovarian metastasis. In a secondary analysis, patients with a primary epithelial ovarian carcinoma were compared with those with an ovarian metastasis.

Univariate analysis of ultrasound and clinical parameters was performed in order to identify parameters statistically significant in differentiating the two groups. Mann–Whitney and chi-square tests were used as appropriate. CA125/CEA ratio was calculated for each patient.

Receiver–operating characteristics (ROC) curves were constructed for CA125, CEA and CA125/CEA in order to evaluate, by means of the area under the curve (AUC), their diagnostic ability to differentiate between the two groups. The ROC curves were also used to determine mathematically the best cut-off value for CEA and CA125/CEA ratio, which was defined as that corresponding to the point on the ROC curve situated farthest from the reference line. For each optimal cut-off value, the accuracy, sensitivity, specificity, positive (LR+) and negative (LR−) likelihood ratios, and positive (PPV) and negative (NPV) predictive values were calculated.

Statistical analysis was performed using R statistics software (R version 3.3.1). Two-sided tests were used and the significance level was set at $P < 0.05$.

RESULTS

Three hundred and ninety-six patients were identified, of which 350 (88.4%) had an ovarian neoplasm and 46 (11.6%) had an ovarian metastasis. The majority of ovarian neoplasms were primary epithelial ovarian carcinomas (197/350, 56%) (Table 1). Most ovarian metastases originated from colon-rectum (25/46, 54%), and many of them had mucinous histology (22/46, 47.8%) (Table 2). Patients with a benign or primary malignant ovarian neoplasm (median age, 55 (range, 15–88) years) were younger than those with an ovarian metastasis (median age, 62 (range, 37–82) years) ($P = 0.016$). Other demographic data, clinical parameters and previous surgical history are detailed in Table 3.

Table 1 Histological findings in 350 patients with benign or primary malignant ovarian neoplasm described as multilocular cyst (five or more locules) or multilocular-solid mass

Histology	*Value*
Benign	99 (28.3)
Endometrioma	10
Teratoma	9
Simple cyst/inclusion cyst	3
Functional cyst	1
Hydrosalpinx/salpingitis	1
Abscess/pelvic inflammatory disease	3
Fibroma	3
Serous cystoadenoma	12
Cystoadenofibroma	27
Mucinous cystoadenoma	27
Other	3
Borderline	43 (12.3)
Invasive	208 (59.4)
Primary epithelial ovarian cancer	197
Malignant rare tumor	7
Other	4

Data are given as *n* (%) or *n*.

Tumor marker values and ultrasound characteristics of the ovarian neoplasms (benign and primary malignant ovarian neoplasms) and ovarian metastases are shown in Table 4. Ovarian neoplasms were smaller than ovarian metastases (median largest diameter, 97 (range, 20–387) mm *vs* 146 (range, 43–259) mm; $P < 0.0001$) and presented with a lower number of ovarian masses with > 10 locules (18.9% *vs* 54.3%; $P < 0.0001$).

The distribution of ultrasound morphologies (multilocular with five or more locules and multilocular-solid) was similar between the two groups: 70/350 (20%) ovarian neoplasms (53 benign, nine borderline and eight invasive) and 12/46 (26.1%) ovarian metastases were multilocular, whereas 280/350 (80%) ovarian neoplasms (46 benign, 34 borderline and 200 invasive) and 34/46 (73.9%) ovarian metastases were multilocular-solid (Figure 1). Papillary projections were reported more frequently in ovarian neoplasms than in ovarian metastases (76/350 *vs* 2/46 (21.7% *vs* 4.3%); $P = 0.003$).

Tumor marker values and ultrasound characteristics of primary epithelial ovarian carcinomas are shown in Table 4. The majority of both primary epithelial ovarian carcinomas (191/197 (97%)) and ovarian metastases (34/46 (73.9%)) were multilocular-solid masses; however, fewer primary epithelial ovarian carcinomas were described as multilocular than were ovarian metastases (6/197 *vs* 12/46 (3% *vs* 26.1%); $P < 0.0001$). Fewer tumors containing > 10 locules were found in the primary epithelial ovarian carcinoma group (35/197 (17.8%)) than in the metastatic group (25/46 (54.3%); $P < 0.0001$). Papillary projections were reported in 34/197 (17.3%) primary epithelial ovarian

Table 2 Clinical and histological findings in patients with ovarian metastasis with multilocular cyst (five or more locules) or multilocular-solid mass, overall and according to whether tumor was synchronous or metachronous

Characteristic	*All* (n = *46*)	*Synchronous* (n = *31*)	*Metachronous* (n = *15*)
Age at diagnosis of primary tumor (years)	56.5 (37–82)	59 (37–82)	56 (39–74)
Age at diagnosis of ovarian metastasis (years)	—	—	63 (41–79)
DFI (months)	—	—	24 (7–264)
Mode of histological diagnosis of metastasis			
Radical surgery	29 (63)	22 (71)	7 (46.7)
Tru-cut biopsy	17 (37)	9 (29)	8 (53.3)
Origin and histotype			
Mucinous adenocarcinoma of small bowel	1 (2.2)	0 (0)	1 (6.7)*
Mucinous adenocarcinoma of appendix	1 (2.2)	1 (3.2)	0 (0)
Low-grade appendiceal mucinous neoplasm	3 (6.5)	3 (9.7)	0 (0)
Mucinous adenocarcinoma of cecum	1 (2.2)	0 (0)	1 (6.7)†
Adenocarcinoma of cecum	1 (2.2)	1 (3.2)	0 (0)
Mucinous adenocarcinoma of colon	7 (15.2)	5 (16.1)	2 (13.3)‡
Adenocarcinoma of colon	9 (19.6)	6 (19.4)	3 (20)§
Mucinous adenocarcinoma of sigma	3 (6.5)	1 (3.2)	2 (13.3)¶
Gastrointestinal stromal tumor of sigma	1 (2.2)	1 (3.2)	0 (0)
Mucinous adenocarcinoma of rectum	3 (6.5)	0 (0)	3 (20.0)**
Mucinous adenocarcinoma of biliopancreatic tract	5 (10.9)	5 (16.1)	0 (0)
Invasive ductal carcinoma of breast	1 (2.2)	0 (0)	1 (6.7)††
Invasive lobular carcinoma of breast	1 (2.2)	0 (0)	1 (6.7)‡‡
Adenocarinoma of lung	1 (2.2)	0 (0)	1 (6.7)§§
Mucinous adenocarcinoma of cervix	1 (2.2)	1 (3.2)	0 (0)
Cervical adenocarcinoma	2 (4.3)	2 (6.5)	0 (0)
Endometrioid adenocarcinoma of endometrium	2 (4.3)	2 (6.5)	0 (0)
Serous carcinoma of endometrium	1 (2.2)	1 (3.2)	0 (0)
Endometrial stroma sarcoma	1 (2.2)	1 (3.2)	0 (0)
Carcinoma of stomach	1 (2.2)	1 (3.2)	0 (0)

Data are given as median (range) or *n* (%). *Age at first diagnosis, 55 years; DFI, 20 months. †Age at first diagnosis, 74 years; DFI, 17 months. ‡Median age at first diagnosis, 58 (range, 53–63) years; median DFI, 9.5 (range, 8–11) months. §Median age at first diagnosis, 58 (range, 51–65) years; median DFI, 25 (range, 24–58) months. ¶Median age at first diagnosis, 48.5 (range, 40–57) years; median DFI, 38 (range, 11–65) months. **Median age at first diagnosis, 56 (range, 48–69) years; median DFI, 24 (range, 7–264) months. ††Age at first diagnosis, 58 years; DFI, 122 months. ‡‡Age at first diagnosis, 39 years; DFI, 75 months. §§Age at first diagnosis, 53 years; DFI, 7 months. DFI, disease-free interval (time between first diagnosis and ovarian metastasis).

Table 3 Clinical characteristics of 396 patients with multilocular ovarian cyst (five or more locules) or multilocular-solid ovarian mass, according to whether tumor was neoplasm or metastasis

Characteristic	*Ovarian neoplasm** (n = *350*)	*Ovarian metastasis* (n = *46*)	P
Age at diagnosis of ovarian mass (years)	55 (15–88)	62 (37–82)	0.016
Nulliparous†	58/197 (29.4)	5/26 (19.2)	0.553
Personal history of ovarian cancer	8 (2.3)	1 (2.2)	0.962
Personal history of breast cancer‡	21/269 (7.8)	1/31 (3.2)	0.354
Postmenopausal§	209/348 (60.1)	31/45 (68.9)	0.252
Previous surgery			
Hysterectomy	21 (6.0)	2 (4.3)	0.652
Oophorectomy	11 (3.1)	2 (4.3)	0.243
Current hormonal therapy	6 (1.7)	0 (0)	0.371
Symptoms¶	121/255 (47.5)	11/30 (36.7)	0.312
Type of symptom**			0.664
Pain	69/111 (62.2)	5/10 (50.0)	
Abdominal bloating	18/111 (16.2)	2/10 (20.0)	
Abnormal bleeding	5/111 (4.5)	0/10 (0)	
Other	19/111 (17.1)	3/10 (30.0)	

Results are given as median (range), *n*/*N*(%) or *n* (%). *Includes benign and primary malignant ovarian neoplasms. Information available for: †223 cases; ‡300 cases; §393 cases; ¶285 cases; **121/132 cases.

carcinomas and in 2/46 (4.3%) ovarian metastases ($P = 0.035$).

ROC curve analysis of CA125, CEA and CA125/CEA in the whole study population is shown in Figure 2. The best cut-off value of CA125 for distinguishing between ovarian neoplasms and ovarian metastases was 265.9 U/mL. The predictive performance of this CA125 cut-off value was as follows: AUC, 0.559 (95% CI, 0.478–0.639); accuracy, 41.2%; sensitivity, 35.7%; specificity, 82.6%; PPV, 94%; and NPV, 14.4%. The best cut-off value of CEA for distinguishing ovarian neoplasms from ovarian metastases was 2.33 ng/mL. The predictive performance of this CEA cut-off value was as follows: AUC, 0.791 (95% CI, 0.711–0.870); accuracy, 73.7%; sensitivity, 73.1%; specificity, 78.3%; PPV, 96.2%; and NPV, 27.7%. The best cut-off value of the CA125/CEA ratio for distinguishing between ovarian neoplasms and ovarian metastases was 11.92. The predictive performance of this CA125/CEA cut-off value was as follows: AUC, 0.758 (95% CI, 0.683–0.833); accuracy, 79.8%; sensitivity, 82.3%; specificity, 60.9%; PPV, 94.1%; and NPV, 31.1% (Figure 2).

When considering only primary epithelial ovarian carcinomas and ovarian metastases, ROC curve analysis showed that the best cut-off value of CA125 for distinguishing primary epithelial ovarian carcinomas from

Table 4 Tumor markers and ultrasound findings in 396 patients with multilocular ovarian cyst (five or more locules) or multilocular-solid ovarian mass, according to whether mass was neoplasm or metastasis

	Ovarian neoplasm				
Characteristic	*All** *(n = 350)*	*Primary epithelial ovarian carcinoma (n = 197)*	*Ovarian metastasis (n = 46)*	P†	P‡
CA125 (U/mL)	110.2 (2.4–25 000)	334.3 (5.5–25 000)	67.3 (7–4938.7)	0.197	< 0.0001
CEA (ng/mL)	1.4 (0.2–132)	1.4 (0.2–132)	7.2 (0.5–15 000)	< 0.0001	< 0.0001
CA125/CEA	54.1 (0.6–31 645.6)	186.2 (1.2–31 645.6)	9.1 (0.1–369.3)	< 0.0001	< 0.0001
Largest diameter of lesion (mm)	97 (20–387)	112 (22–290)	146 (43–259)	< 0.0001	0.009
Type of tumor				0.338	< 0.0001
Multilocular (≥ 5 locules)	70 (20.0)	6 (3.0)	12 (26.1)		
Multilocular solid	280 (80.0)	191 (97.0)	34 (73.9)		
Number of locules				< 0.0001	< 0.0001
2	29 (8.3)	14 (7.1)	1 (2.2)		
3	32 (9.1)	25 (12.7)	0 (0)		
4–10	223 (63.7)	123 (62.4)	20 (43.5)		
> 10	66 (18.9)	35 (17.8)	25 (54.3)		
Echogenicity of cyst fluid				0.084	0.193
Anechoic	105 (30.0)	53 (26.9)	8 (17.4)		
Low level	190 (54.3)	113 (57.4)	35 (76.1)		
Ground glass	35 (10.0)	19 (9.6)	2 (4.3)		
Hemorrhagic	6 (1.7)	5 (2.5)	0 (0)		
Mixed	14 (4.0)	7 (3.6)	1 (2.2)		
Largest solid component (mm)§	45 (1–165)	51 (6–160)	58 (12–120)	0.149	0.222
Presence of papillary projection(s)	76 (21.7)	34 (17.3)	2 (4.3)	0.003	0.035
Number of papillary projections if papillations present¶				0.143	0.154
1	27/75 (36.0)	10/34 (29.4)	0/2 (0)		
2	13/75 (17.3)	2/34 (5.9)	1/2 (50.0)		
3	4/75 (5.3)	1/34 (2.9)	0/2 (0)		
> 3	31/75 (41.3)	21/34 (61.8)	1/2 (50.0)		
Height of largest papillary projection (mm)	11.5 (3–57)	11 (3–57)	15.5 (12–19)	0.007	0.030
Papillation flow if papillations present	48/76 (63.2)	27/34 (79.4)	2/2 (100)	0.096	0.126
Irregular internal cyst walls**	158/301 (52.5)	107/177 (60.5)	18/46 (39.1)	0.005	0.002
Shadow	35 (10.0)	7 (3.6)	0 (0)	0.023	0.353
Incomplete septum	16 (4.6)	6 (3.0)	1 (2.2)	0.706	1.000
Free fluid in pouch of Douglas	118 (33.7)	88 (44.7)	14 (30.4)	0.657	0.078
Ascites	60 (17.1)	56 (28.4)	8 (17.4)	0.966	0.126
Bilateral tumor	108 (30.9)	77 (39.1)	14 (30.4)	0.953	0.275
Metastases††	113 (32.3)	89 (45.2)	15 (32.6)		
Color score				0.034	0.015
1	37 (10.6)	2 (1.0)	1 (2.2)		
2	73 (20.9)	27 (13.7)	8 (17.4)		
3	126 (36)	70 (35.5)	26 (56.5)		
4	114 (32.6)	98 (49.7)	11 (23.9)		
Diagnosis on the basis of subjective assessment				0.014	0.321
Benign	74 (21.1)	3 (1.5)	2 (4.3)		
Borderline	50 (14.3)	8 (4.1)	4 (8.7)		
Malignant	223 (63.7)	185 (93.9)	40 (87.0)		
Not possible	3 (0.9)	1 (0.5)	0 (0)		

Data are given as median (range), *n* (%) or *n*/*N* (%). *Includes benign and primary malignant ovarian neoplasms. †All ovarian neoplasms *vs* ovarian metastases. ‡Primary epithelial ovarian carcinomas *vs* ovarian metastases. §Solid component includes papillary projections. ¶Information available for 77/78 cases for all neoplasms *vs* metastases. **Information available for 347/396 cases for all neoplasms *vs* metastases and for 223/243 cases for primary epithelial carcinomas *vs* metastases. ††Other than of the ovaries.

ovarian metastases was also 265.9 U/mL (Figure 3). The predictive performance of this CA125 cut-off value was as follows: AUC, 0.735 (95% CI, 0.657–0.813); accuracy, 62.1%; sensitivity, 57.4%; specificity, 82.6%; PPV, 93.4%; and NPV, 31.1%. The best cut-off value of CEA for distinguishing primary epithelial ovarian carcinomas from ovarian metastases was 2.33 ng/mL. The predictive performance of this CEA cut-off value was as follows: AUC, 0.781 (95% CI, 0.700–0.862); accuracy, 73.7%; sensitivity, 72.6%; specificity, 78.3%; PPV, 93.5%; and NPV, 40%. The best cut-off value of CA125/CEA ratio for distinguishing primary epithelial ovarian carcinomas from ovarian metastases was 19.7. The predictive performance of this CA125/CEA cut-off value was as follows:

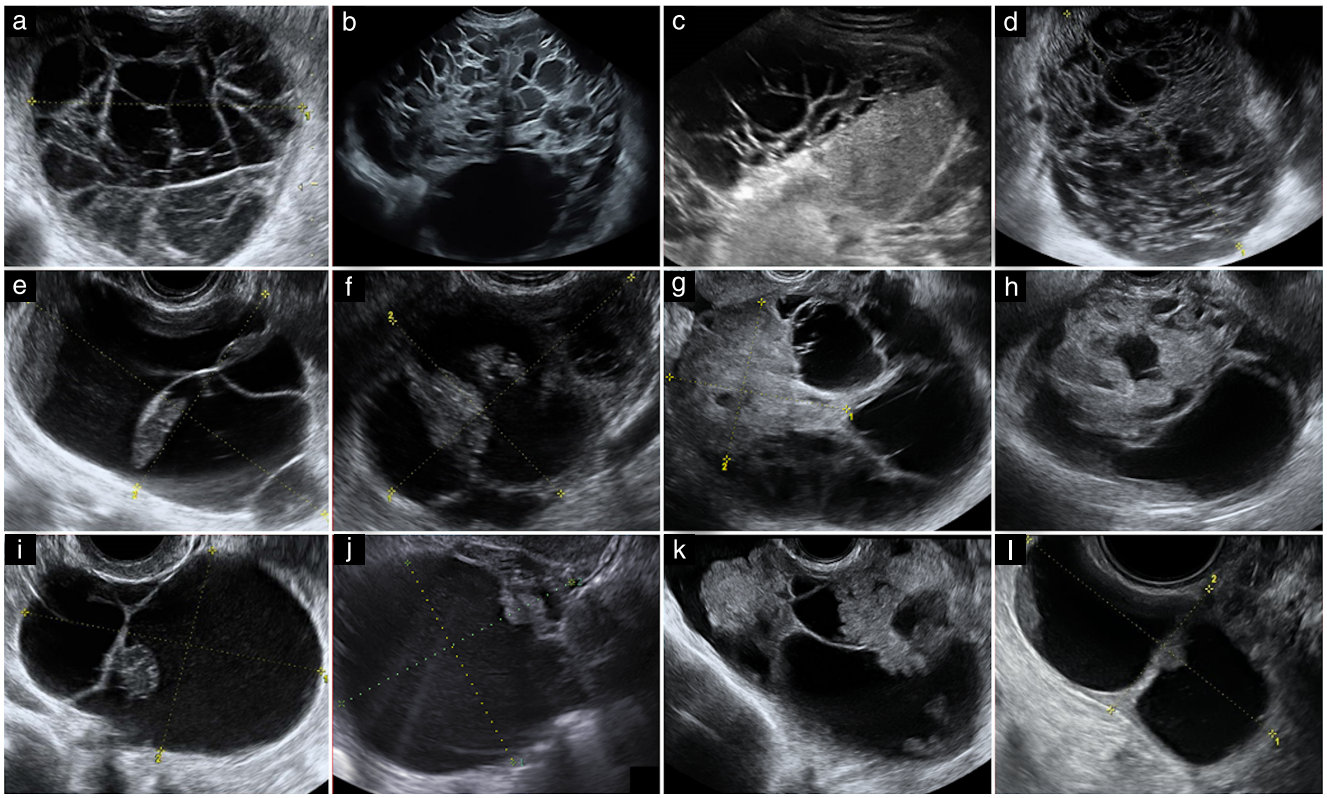

Figure 1 Ultrasound images of multilocular masses (benign (a), borderline (b) and primary epithelial (c) ovarian carcinomas and ovarian metastasis (d)), multilocular-solid masses (benign (e), borderline (f) and primary epithelial (g) ovarian carcinomas and ovarian metastasis (h)), and multilocular-solid masses with papillary projections (benign (i), borderline (j) and primary epithelial (k) ovarian carcinomas and ovarian metastasis (l)).

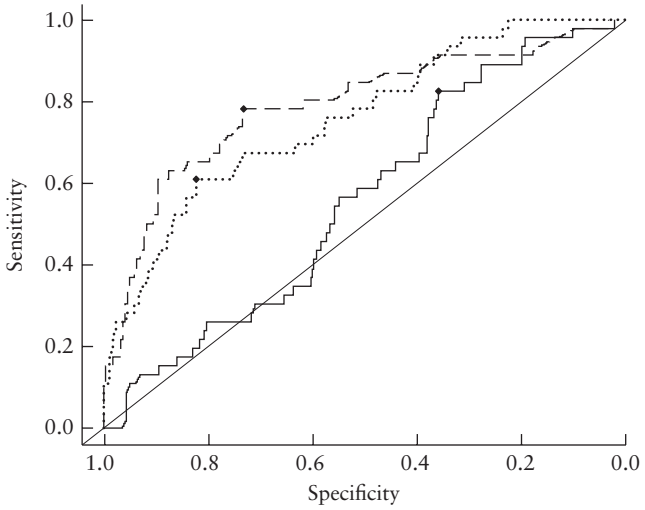

Figure 2 Receiver–operating characteristics curves for CA125 (——), CEA (— —) and CA125/CEA (·····) in differentiating between ovarian neoplasms (including benign and primary malignant) and ovarian metastases in 396 women with multilocular or multilocular-solid ovarian mass. CA125 optimal cut-off is 265.9 U/mL (area under the curve (AUC), 0.559 (95% CI, 0.478–0.639)) with specificity of 0.357 and sensitivity of 0.826. CEA optimal cut-off is 2.33 ng/mL (AUC, 0.791 (95% CI, 0.711–0.870)) with sensitivity of 0.731 and specificity of 0.783. CA125/CEA optimal cut-off is 11.92 (AUC, 0.758 (95% CI, 0.683–0.833)) with sensitivity of 0.823 and specificity of 0.609.

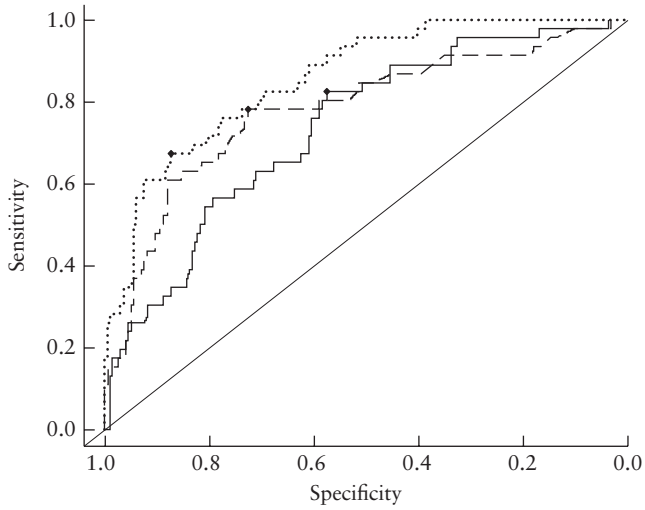

Figure 3 Receiver–operating characteristics curves for CA125 (——), CEA (— —) and CA125/CEA (·····) in differentiating between primary epithelial ovarian carcinomas and ovarian metastases in 396 women with multilocular or multilocular-solid ovarian mass. CA125 optimal cut-off is 265.9 U/mL (area under the curve (AUC), 0.735 (95% CI, 0.657–0.813)) with sensitivity of 0.574 and specificity of 0.826. CEA optimal cut-off is 2.33 ng/mL (AUC, 0.781 (95% CI, 0.700–0.862)) with sensitivity of 0.726 and specificity of 0.783. CA125/CEA optimal cut-off is 19.7 (AUC, 0.856 (95% CI, 0.800–0.913)) with sensitivity of 0.873 and specificity of 0.674.

AUC, 0.856 (95% CI, 0.800–0.913); accuracy, 83.5%; sensitivity, 87.3%; specificity 67.4%; PPV, 92%; and NPV, 55.4% (Figure 3).

DISCUSSION

The present study compared ultrasound features and tumor markers of ovarian neoplasms (including benign and primary malignant) and ovarian metastases in patients with an ultrasound diagnosis of an ovarian mass with multilocular (five or more locules) or multilocular-solid morphology. In this selected population, the prevalence of ovarian metastases was 11.6%, most of which were derived from an intestinal primary tumor and were of mucinous histology. On ultrasound examination, ovarian metastases were significantly larger than ovarian neoplasms, presenting with more than 10 locules in most cases. The ovarian metastases were also characterized by the absence of papillary projections. With regards to tumor markers, CEA alone and CA125/CEA demonstrated better performance than did CA125 to discriminate between ovarian neoplasms (including benign and malignant) and ovarian metastases, and the best cut-off values of CEA and CA125/CEA were 2.33 ng/mL and 11.92, respectively.

To our knowledge, no studies have thus far assessed the role of ultrasound characteristics and clinical parameters in identifying ovarian metastases in multilocular or multilocular-solid ovarian masses. The strength of this study is the large number of patients recruited from the three centers. This allowed us to investigate an extensive panorama of histological entities presenting with the same ultrasound morphology. Moreover, the standardized clinical and ultrasound analysis method provided homogeneous information for all patients. Yet, this study has some limitations. The retrospective nature of the analysis is the main limitation. An important bias is also represented by the fact that only cases having CA125 and CEA measured at diagnosis were included. Finally, the involvement of three referral oncology centers may have led to a high prevalence of malignant neoplastic diseases.

Our results mainly confirmed the ultrasound features of ovarian metastases from tumors of the colon-rectum, biliary tract, appendix and pancreas that have been reported in other studies, such as large multilocular-solid lesions in most cases, with a high number of locules and papillary projections in a very low number of cases[6–8]. However, we reported that a conspicuous number (26.1%) of ovarian metastases appeared purely as multilocular tumors without a solid component. This could be explained by the presence in the current series of masses originating from the appendix (low-grade appendiceal mucinous neoplasms) or from the biliary tract.

Surprisingly, a considerable number of benign masses (i.e. teratoma, abscess, simple cyst and endometrioma) were observed in the present study. These histological categories usually show typical ultrasound features, such as unilocular morphology, multilocular with a few locules and ground glass cyst content, that make these masses easy to diagnose using subjective assessment. However, we acknowledge that they appear atypical in some cases[23,24]; additional clinical and ultrasound parameters, such as absence of vascularization in solid component, age and ground glass content, might help physicians to reach the proper diagnosis.

Regarding ovarian tumor marker assessment, other studies investigated the discriminating role of the CA125/CEA ratio[16,17]; however, these studies considered different series, analyzing only primary malignant ovarian neoplasms *vs* ovarian metastases, and they found a higher optimal cut-off level (CA125/CEA > 25) than in the current study.

In our series, including all ovarian masses with multilocular (five or more locules) and those with multilocular-solid morphology, both CA125/CEA and CEA alone showed moderate accuracy in differentiating between ovarian metastases and benign and primary malignant ovarian neoplasms.

The opportunity to distinguish preoperatively ovarian metastases from ovarian neoplasms can be clinically useful, as they require different clinical and surgical management. Suspicion of ovarian metastasis will prompt other diagnostic procedures before surgery to pinpoint the origin of the primary tumor, as well as to plan the most appropriate surgical procedure and an adequate surgical team.

In conclusion, CA125/CEA and CEA alone did not show any significant difference in distinguishing between ovarian neoplasms (including benign and malignant) and ovarian metastases in masses with multilocular or multilocular-solid morphology. Therefore, in this morphological subgroup of ovarian masses, CEA alone is sufficient for differentiating between them.

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