Imaging in gynecological disease: clinical and ultrasound characteristics of ovarian embryonal carcinomas, non-gestational choriocarcinomas and malignant mixed germ cell tumors

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What are the novel findings of this work?

Ultrasound characteristics of rare germ cell tumors are poorly described. The present study described the clinical and ultrasound characteristics of three rare malignant ovarian germ cell tumors: embryonal carcinoma, non-gestational choriocarcinoma and malignant mixed germ cell tumor.

What are the clinical implications of this work?

Knowledge of the clinical and ultrasound features of germ cell tumors helps clinicians identify or suspect these neoplasms. The ultrasound pattern of embryonal carcinomas, choriocarcinomas, and mixed germ cells tumors differs from that of epithelial ovarian cancers and from other germ cell tumors.

Abstract

Objective To describe the clinical and ultrasound characteristics of three rare malignant ovarian germ cell tumors: embryonal carcinoma, non-gestational choriocarcinoma and malignant mixed germ cell tumor.

Methods This is a retrospective multicenter study. From the International Ovarian Tumor Analysis (IOTA) database, we identified seven patients with a histological diagnosis of ovarian embryonal carcinoma, non-gestational choriocarcinomas and malignant mixed germ cell tumors, who had undergone preoperative ultrasound examination by an experienced ultrasound examiner between 2000 and 2020. Another six patients with the same histology were identified from the databases of gynecological oncology in the participating centers. All tumors were described using IOTA terminology. Three authors reviewed all available ultrasound images and described them using pattern recognition.

Results One patient with embryonal carcinoma, five patients with non-gestational ovarian choriocarcinoma, and seven patients with ovarian malignant mixed germ cell tumors (six primary tumors and one recurrence) were identified. The median age at diagnosis was 26 (range 14 to 77) years. Beta-human chorionic gonadotropin (hCG) levels were highest in non-gestational choriocarcinomas, alfa-fetoprotein (AFP) levels were highest in malignant mixed germ cell tumors. Most tumors were FIGO Stage I (9/12, 75.0%). All tumors were unilateral, and the median largest diameter was 129 (range 38-216) mm. 11/13 (84.6%) were solid tumors and 2/13 (15.4 %) were

multilocular-solid tumors; 9/13 (69.2%) manifested abundant vascularization at color Doppler examination. Using pattern recognition, the typical ultrasound feature was that of a large solid tumor with inhomogeneous echogenicity of the solid tissue and often dispersed cysts, the cysts in most cases being small and irregular. Some tumors had smooth contours, others had irregular contour.

Conclusions A unilateral, large solid tumor with inhomogeneous echogenicity of the solid tissue, and with dispersed small cystic areas, in a young woman should raise the suspicion of a rare malignant germ cell tumor. This suspicion can guide the clinician to test tumor markers specific for malignant germ cell tumors.

Introduction

Aim

The aim is to supplement the Imaging in gynecological disease series on ovarian germ cell tumors by describing the clinical and ultrasound characteristics of three rare malignant ovarian germ cell tumors: embryonal carcinoma, non-gestational choriocarcinoma and malignant mixed germ cell tumor.

Epidemiology

Ovarian germ cell tumors arise from primordial germ cells of the ovary. They are the second most frequently described ovarian neoplasms following epithelial tumors, and they can have a benign or malignant behavior. Benign mature teratomas constitute nearly 95% of all germ cell tumors. The remaining five percent are considered malignant. The most common subtypes of malignant germ cell tumors are dysgerminoma, immature teratoma, and yolk sac tumors. Embryonal carcinoma, choriocarcinoma and mixed germ cell tumors are very rare subtypes.¹

Embryonal carcinoma in the ovary was first described by Kurman and Norris in 1976 as a separate malignant germ cell neoplasm.² It is often mixed with other neoplastic germ cell components.³⁻⁴ Embryonal carcinomas are reported to account for about 4% of ovarian malignant

germ cell tumors.⁵ They occur predominantly in adolescents and young women with an average age of 15 years.²

Choriocarcinoma of the ovary may be: 1) a primary gestational choriocarcinoma originating in an ovarian pregnancy, 2) a metastasis from a primary gestational choriocarcinoma arising in other parts of the genital tract, usually the uterus, or 3) a primary germ cell tumor differentiating in the direction of trophoblastic structures, often admixed with other neoplastic germ cell elements. This means that choriocarcinoma of the ovary may be divided into two groups: 1) gestational choriocarcinoma comprising the first two groups described above and 2) non-gestational choriocarcinoma, i.e. a germ cell tumor differentiating towards trophoblastic structures.⁶ Ovarian choriocarcinoma is reported to account for 2% of ovarian malignant germ cell tumors.⁵ Non-gestational ovarian choriocarcinoma typically affects children and young adults, rarely it may be diagnosed in postmenopausal women.⁷⁻⁹ Non-gestational choriocarcinomas have poorer prognosis than gestational choriocarcinomas.¹⁰

Ovarian malignant mixed germ cell tumors are rare neoplasms containing different proportions of malignant germ cell elements.¹¹ They originate from the primitive germ cells of the embryonic gonad and are reported to account for 8% of all malignant germ cell tumors.¹² The most common components of these mixed tumors are, in order of frequency, dysgerminoma, yolk sac tumor, immature teratoma, choriocarcinoma and embryonal carcinoma. The most frequent combination is dysgerminoma and yolk sac tumor.¹³⁻¹⁴ These neoplasms are often diagnosed in the first two decades of life with the highest incidence in women 15–19 years old.⁵

Microscopy

Embryonal carcinoma is characterized by malignant cell growth in sheets or nests. Glands are frequent, papillae are uncommon. Blood vessel invasion is common. The embryonal carcinoma cells are often positive for cytokeratin AE1/AE3, cluster differentiation 30 (CD30), Octamer-binding transcription 3/4 (OCT3/4), Sal-like protein 4 (SALL4) and glypican 3, while transcription factor SOX2 positivity has been reported to be variable.¹⁵⁻¹⁶ If syncytiotrophoblastic cells are present, they are cytokeratin and human chorionic gonadotropin (hCG) positive.¹¹

Like gestational choriocarcinomas, non-gestational choriocarcinomas are composed of a mixture of giant syncytiotrophoblastic and mononucleate trophoblastic cells, frequently associated with hemorrhage on an extensively necrotic background.¹² Vascular invasion is common.¹⁷

Choriocarcinomas may stain for cytokeratin, hCG, alpha inhibin and glypican 3. Distinguishing between gestational and non-gestational choriocarcinoma is important because these two tumor types have distinct clinical behavior, different sensitivity to chemotherapy and different prognosis. DNA polymorphism analysis has been described as a useful tool to distinguish between gestational and non-gestational choriocarcinoma. Tumors of gestational origin have paternal genomic contributions, whereas non-gestational tumors have genomes only of maternal origin and do not possess any alleles derived from the male partner of the patient. However, because DNA analysis is expensive and may not be available in all medical centers, their use is limited.¹⁸

Malignant mixed germ cell tumors of the ovary are composed of a mixture of germ cell neoplasms. If two or more components are present, they may be intimately blended or may constitute separate entities within the tumor. The most common germ cell tumor elements are dysgerminoma (80%), yolk sac tumor (70%), immature teratoma (53%), choriocarcinoma (20%),

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and embryonal carcinoma (13%).¹⁹ Syncytiotrophoblasts may be found either as a part of a choriocarcinoma or as individual elements. Embryonal carcinoma epithelium or yolk sac cells may be mixed with embryoid bodies, which are a component of immature teratoma. The immunomarkers OCT4, CD30, growth differentiation Factor 3 (GDF3) and glypican 3 can help characterize the tumor components.^{16,20}

Macroscopy

All three types of malignant germ cell tumors are typically large, unilateral, solid neoplasms with cystic spaces inside.¹² They usually have a smooth outer surface with multiple areas of hemorrhage and necrosis.¹² However, the appearance of the cut surface of the malignant mixed germ cell tumor varies depending on the different germ cell tumors present.¹⁷

Clinical features

Clinical symptoms of the three types of rare malignant germ cell tumors are abdominal or pelvic pain and palpable abdominal mass. Menstrual abnormalities and endocrine disorders like precocious puberty have been described, in particular in women with non-gestational choriocarcinoma or embryonal carcinoma.²¹⁻²³ Conditions to be considered in the differential diagnosis in young women include ectopic pregnancy²⁴ (especially in patients with non-gestational choriocarcinomas, because of the increased levels of serum-hCG) but also adnexal torsion, hemorrhagic ovarian cyst and tubo-ovarian abscess.²³⁻²⁴ Depending on the type of germ cell tumor, different serum markers may be elevated. Mixed malignant germ cell tumors may secrete beta-hCG (if they contain choriocarcinoma cells), alfa-fetoprotein (AFP) (if they contain yolk sac germ cells) or lactate dehydrogenase (LDH) (if they contain dysgerminoma cells).^{12,17,21,25} Typically, non-gestational choriocarcinomas secrete beta-hCG.^{1,6,12} Embryonal carcinomas may secrete both AFP and beta-hCG.^{2,6}

Prognosis

Most malignant germ cell tumors are diagnosed at an early stage. In 60-70% of cases the FIGO stage is IA-II, in 20-30% FIGO stage III, and only in a small fraction FIGO stage IV.² Ovarian germ cell tumors frequently disseminate through the lymphatic system.²¹

Treatment for these three types of rare germ cell tumors is surgery plus adjuvant chemotherapy. Adjuvant chemotherapy is the standard of care for women with germ cell malignancies except for those with stage IA dysgerminoma or stage IA grade 1 immature teratoma.²⁶⁻²⁸ For young women who want to preserve their fertility, unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus followed by chemotherapy is standard treatment.²⁸ Because of the high chemosensitivity of germ cell tumors, lymphadenectomy is not recommended unless there is evidence of abnormal lymph nodes. The most common adjuvant chemotherapy regimen used in these patients is a combination of bleomycin, etoposide, and cisplatin (BEP).²⁷⁻²⁸

The most important prognostic factors of malignant germ cell tumors are FIGO stage, level of tumor markers (high levels entail poor prognosis), histology and grade, and residual disease after surgery.²⁹

Data on survival of ovarian embryonal carcinomas, non-gestational choriocarcinomas and mixed malignant germ cell tumors are limited due to the rarity of these tumors. The 5-year overall survival for all ovarian non-dysgerminoma germ cell tumors has been reported to be 78%,³⁰⁻³¹ that for ovarian embryonal carcinoma 39-100%^{2,29} and that for ovarian mixed malignant germ cell tumors 66.7%.³² A 3-year overall survival of 25-100%, depending on the tumor stage, has been reported for ovarian non-gestational choriocarcinomas.¹⁰

Methods

This is a retrospective multicenter study. From the International Ovarian Tumor Analysis (IOTA) database we identified patients with a histological diagnosis of ovarian embryonal carcinoma, ovarian malignant mixed germ cell tumor, or ovarian non-gestational choriocarcinoma, who had undergone preoperative ultrasound examination by an experienced ultrasound examiner between 2000 and 2020 (IOTA phase 1, 1b, 2, 3 and 5).³³⁻³⁷ Additional patients with the same histology, and with available ultrasound images who had been investigated outside the IOTA studies between 2000 and 2020 were retrospectively identified from the databases of the departments of gynecological oncology of the participating centers (Table 1).

All patients had been preoperatively examined with transvaginal or transrectal and/or abdominal ultrasound using a standardized examination technique.³⁸ All the ultrasound examiners had more than 10 years' experience in gynecological ultrasound, and the ultrasound examinations were carried out using high-end ultrasound equipment. The frequency of the vaginal probes varied between 5.0 and 9.0 MHz and that of the abdominal probes between 3.5 and 5.0 MHz.

For women included in the IOTA studies, clinical and ultrasound information was obtained from the IOTA databases containing prospectively collected data. For women who had been examined outside the IOTA studies, and in case of missing information in the IOTA database, information was retrospectively retrieved from the patients' medical records and entered into an excel file by the principal investigator at each center. Information on final histology, tumor grade, FIGO stage, and tumor markers was recorded. In case of bilateral adnexal masses, the mass with the most complex ultrasound morphology was used in our analysis. If both masses had similar ultrasound morphology

the largest mass or the one most easily accessible with ultrasound was included. The masses were described using the terms and definitions published by the IOTA group.³⁸ Papillary projections were defined as projections of solid tissue into a cyst cavity, arising from the cyst wall or from a septum, with a height ≥ 3 mm. The largest solid component other than a papillary projection (i.e. a solid component not protruding into the cyst cavity) was also measured. In accordance with the IOTA consensus statement, if a papillary projection was the largest solid component of a mass, the papillary projection was recorded and measured both as a papillary projection and as the largest solid component.³⁸ The presence of ascites and fluid in the pouch of Douglas was noted. The vascularization of the tumors on color or power Doppler was described using the IOTA color score: no detectable blood flow (color score=1), minimal blood flow (color score=2), moderate blood flow (color score=3), or abundant blood flow (color score=4). The specific diagnosis made using subjective assessment and suggested by the original ultrasound examiner in the original ultrasound report was recorded.

In addition to using the information collected in the IOTA database and in the patients' medical records, three of the authors (FM, AT, LV), who all had more than 10 years' experience in gynecological ultrasound, together assessed available ultrasound images of ovarian malignant mixed germ cell tumors, non-gestational choriocarcinoma and embryonal carcinoma using pattern recognition with the aim to identify typical ultrasound patterns.³⁹ All clinical and ultrasound data were entered into a dedicated Excel file (Microsoft Office Excel 2019, Redmond, WA, USA). Results are presented as absolute frequency (percentage) for nominal variables and as median (range and interquartile range, IQR) for continuous variables.

Results

Thirteen patients with a histological diagnosis of ovarian embryonal carcinoma (one patient), ovarian non-gestational choriocarcinoma (five patients), and ovarian malignant mixed germ cell tumor (six primary tumors and one recurrence in the contralateral ovary) were identified. Seven patients were included in the IOTA studies, another six patients were examined outside the IOTA studies. Demographic background data, level of tumor markers and tumor characteristics are shown in Table 1. The median age at diagnosis was 26 (range 14 to 77) years. It was 18 (14 to 61) years for patients with a malignant mixed germ cell tumor and 36 (17 to 77) years for those with a non-gestational choriocarcinoma. The only patient with embryonal ovarian carcinoma was 16 years old (post-menarche). Ten of 13 (76.9%) patients were premenopausal, and 11/13 (84.6%) were nulliparous. Six of 13 patients (46.1%) presented with lower abdominal pain.

Beta-hCG levels were highest in non-gestational choriocarcinomas, AFP levels were highest in malignant mixed germ cell tumors. Serum CA 125 was > 35 U/mL in three of the nine patients for whom CA125 results were available. Most tumors were FIGO Stage I (9/12, 75.0%), three neoplasms were diagnosed at stage III (3/12, 25.0%), and one patient with a previous salpingo-oophorectomy for ovarian malignant mixed germ cell tumor had a recurrence in the contralateral ovary.

The ultrasound characteristics of the tumors are shown in Table 2. All tumors were unilateral, and the median largest diameter was 129 (range 38-216) mm. In 9/13 (69.2%) tumors the largest diameter was more than 10 cm. All tumors contained solid components: 11/13 (84.6%) were described as solid tumors and 2/13 (18.1 %) as multilocular-solid tumors with 4 -10 cyst locules.

Most tumors (9/13, 69.2%) manifested abundant vascularization (color score 4) at color Doppler examination. Papillary projections were seen in 2/13 (15.4%) masses. In the original ultrasound report, 9/13 (69.2%) masses were classified as malignant: six as malignant germ cell tumor, one as a borderline tumor, one as primary ovarian cancer, and one as a malignant stromal cell tumor. However, in 4/13 cases (30.7%), the ultrasound examiner was uncertain whether the tumor was benign or malignant.

Good quality electronic ultrasound images were available for ten patients (Figures 1-10). On retrospective analysis of these images, all tumors showed similar ultrasound characteristics. The typical ultrasound feature was that of a large solid tumor with inhomogeneous echogenicity of the solid tissue and often dispersed cysts, the cysts in most cases being small and irregular. Some tumors had smooth contours, others had irregular contour.

Discussion

We have described the clinical and ultrasound characteristics of ovarian embryonal carcinoma, non-gestational choriocarcinoma and malignant mixed germ cell tumors. Most tumors were diagnosed in young women and all were unilateral. At ultrasound examination, almost all tumors were solid, except for few tumors being multilocular-solid, and most were richly vascularized at color Doppler examination. At subjective assessment, the vast majority of these tumors were correctly classified as malignant, and a malignant rare germ cell tumor was suspected in six of them. Using pattern recognition, the typical ultrasound image was that of a large solid tumor with inhomogeneous echogenicity of the solid tissue and often dispersed small and irregular cysts.

To the best of our knowledge, this is the largest study describing ultrasound features of ovarian embryonal carcinoma, ovarian non-gestational choriocarcinoma and ovarian malignant mixed germ cell tumor. Another strength is the standardized description of the tumors using IOTA terminology. The study also has limitations. It is retrospective, which means that some clinical information is missing and that ultrasound images were not available for all cases.

Our results match with those reported in textbooks of pathology and other publications in that most tumors were diagnosed in young patients, and in that all were unilateral, most were large and purely solid.^{9-11,25} In our study, three patients (23%) were post-menopausal. Liu et al. found, by reviewing the literature, that 6/39 (15.4%) of patients with non-gestational choriocarcinoma were post-menopausal, whereas the peak incidence was in the adolescent age of 12–25 years.¹⁰ Acute

abdomen resulting from torsion, tumor rupture, or hemoperitoneum, described in rare cases in the literature,¹⁹ was not observed in our study.

We have found no published reports on the ultrasound features of mixed malignant germ cell tumors or embryonal carcinoma. However, Shabaan et al. described the features of malignant mixed germ cell tumors on computed tomography as “solid masses with cystic areas resulting from hemorrhage or necrosis, or a cystic lesion with solid components”.²¹ We have found two case reports describing the ultrasound features of ovarian non-gestational choriocarcinoma. Heo et al described the ultrasound features of one case of non-gestational choriocarcinoma as “a unilateral solid, cystic, heterogeneous lesion”.²² Syed et al reported another case of ovarian non-gestational choriocarcinoma but with bilateral masses.⁴⁰ Bilateral ovarian non-gestational choriocarcinomas are likely to be exceedingly rare.^{1,6,12,21}

Knowledge of the clinical and ultrasound features of germ cell tumors helps clinicians identify or suspect these neoplasms. A unilateral, large solid tumor with inhomogeneous echogenicity of the solid tissue, and with dispersed small irregular cystic areas, in a young woman should raise the suspicion of a rare malignant germ cell tumor, and specific tumor markers (hCG, AFP, LDH) should be investigated. Although we were unable to identify an ultrasound pattern specific for each of the three rare germ cells tumors, the ultrasound pattern of embryonal carcinomas, choriocarcinomas, and mixed germ cells tumors differs from that of dysgerminomas,⁴¹ immature teratomas,⁴² and yolk sac tumors.⁴³ Not all unilateral adnexal solid tumors in young women originate from germ cells, however. Possible differential diagnoses include ovarian stromal cell tumors (Sertoli cell tumor and Sertoli-Leydig cell tumor, granulosa cell tumor)⁴⁴⁻⁴⁵ or epithelial

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malignant tumors (ovarian clear cell carcinoma and endometrioid carcinoma).⁴⁶⁻⁴⁷ However, the mean age at diagnosis of the latter three tumor types is higher than that of women with malignant germ cell tumors.⁴⁵⁻⁴⁷ A unilateral solid tumor in a young woman could also be a metastasis from another primary tumor, but most metastases are bilateral and solid metastases are often smaller than malignant germ cell tumors.⁴⁸

A much larger study than this one is needed for it to be possible to detect differences in the ultrasound appearance between embryonal carcinomas, choriocarcinomas, and mixed germ cells tumor, if there are any. However, preoperative distinction between the three is not crucial from a clinical point of view.

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Figure legends

Figure 1. Gray-scale (a) and Color Doppler (b) images of a malignant mixed germ cell tumor classified as FIGO stage IIIA in an 18-year-old patient. Ultrasound examination showed a left-sided solid tumor, 190x129x182 mm in size, with irregular margins, inhomogeneous echogenicity of the solid tissue and dispersed small irregular cystic areas, richly vascularized on color Doppler.

Figure 2. Gray-scale (a) and Color Doppler (b) images of a malignant mixed germ cell tumor classified as FIGO stage IIIA in a 26-year-old patient. Ultrasound examination showed a left-sided solid tumor, 129x101x88 mm in size, with irregular margins, inhomogeneous echogenicity of the solid tissue and dispersed small irregular cysts, richly vascularized on color Doppler.

Figure 3. Gray-scale (a) and Color Doppler (b) images of a malignant mixed germ cell tumor classified as FIGO stage IA in an 18-year-old patient. Ultrasound examination showed a right-sided solid tumor, 76x66x62 mm in size, with smooth borders, inhomogeneous echogenicity of the solid tissue and dispersed small irregular cysts, richly vascularized on color Doppler.

Figure 4. Gray-scale (a) and Color Doppler (b) images of a malignant mixed germ cell tumor classified as FIGO stage IA in a 14-year-old patient. Ultrasound examination showed a left-sided solid tumor, 51x32x44 mm in size, with smooth borders, inhomogeneous echogenicity of the solid tissue with small cystic areas, moderately vascularized on color Doppler. These images were obtained using transabdominal ultrasound. This makes it difficult to assess details.

Figure 5. Gray-scale (a) and Color Doppler (b) images of a pelvic recurrence of malignant mixed germ cell tumor in a 14-year-old patient. Ultrasound examination showed a solid tumor in the middle of the pelvis, 122x89x137 mm in size, with irregular margins, inhomogeneous echogenicity of the solid tissue and dispersed irregular cysts of moderate size, moderately vascularized on color Doppler.

Figure 6. Gray-scale (a) and Color Doppler (b) images of a non-gestational choriocarcinoma FIGO stage IA in a 36-year-old patient. Ultrasound examination showed a left-sided solid tumor, 44x94x136 mm in size, with smooth borders, inhomogeneous echogenicity of the solid tissue and minute irregular cysts, richly vascularized on color Doppler.

Figure 7. Gray-scale (a) and Color Doppler (b) images of a non-gestational choriocarcinoma FIGO stage IA in a 43-year-old patient. Ultrasound examination showed a right-sided solid tumor, 102x82x90 mm in size, with irregular borders, inhomogeneous echogenicity of the

solid tissue, multiple large cystic areas with smooth borders in the periphery of the tumor, richly vascularized on color Doppler.

Figure 8. Gray-scale (a) and Color Doppler (b) images of a non-gestational choriocarcinoma FIGO stage IA in a 27-year-old patient. Ultrasound examination showed a left-sided solid tumor, 34x23x38 mm in size, with smooth borders, inhomogeneous echogenicity of the solid tissue, richly vascularized on color Doppler. The cystic structures in the periphery are follicles in the normal ovarian stroma (“positive ovarian crescent sign”).

Figure 9. Gray-scale (a) and Color Doppler (b) images of a non-gestational choriocarcinoma FIGO stage IC in a 77-year-old patient. Ultrasound examination showed a right-sided solid tumor, 91x86x84 mm in size, with smooth borders, inhomogeneous echogenicity of the solid tissue and dispersed small irregular cysts, richly vascularized on color Doppler.

Figure 10. Gray-scale (a) and Color Doppler (b) images of an embryonal carcinoma FIGO stage IA in a 16-year-old patient. Ultrasound examination showed a solid tumor in the middle of the pelvis, 216x148x90 mm in size, with irregular margins, inhomogeneous echogenicity of the solid tissue with dispersed irregular cysts, richly vascularized on color Doppler.

Table 1. Clinical and histological characteristics for patients with ovarian malignant mixed germ cell tumor, non-gestational choriocarcinoma and embryonal carcinoma.

Characteristic	All n=13	Malignant mixed germ cell tumor n=7	Non-gestational choriocarcinoma n= 5	Embryonal carcinoma n=1
Age at diagnosis, years	26 [14 to 77 (16.5;51)]	18 [14 to 61 (14;59)]	36 [17 to 77, (22;60)]	16
Nulliparous	11 (84.6)	7 (100)	3 (60)	1
Premenopausal	10 (76.9)	5 (71.4)	4 (80)	1
Current hormonal therapy	0/13	0/7	0/5	0
Previous unilateral salpingo-oophorectomy	2 (15.3)	1 (14.2)	1 (20)	0
LDH serum levels at diagnosis(U/L) ^a	393 [4 to 1146 (115.7;633)]	255.5 [4 to 1146 (41.2;949)]	445 (428-462)	n.a
B-hCG serum levels at diagnosis(mU/mL) ^b	28111 [6 to 600.000 (10;108000)]	6090 [6 to 108.000 (7; 84042)]	57 057 (28.111- 600.000)	n.a.
AFP serum levels at diagnosis (ng/mL) ^a	5567.5 [2 to 55331(11;35538)]	20.020 [2 to 55331 (2776;48733)]	24.5 (14-35)	n.a.
CA 125 serum levels at diagnosis(U/mL) ^c	12 [3 to 494 (8.5;378)]	10.5 [3 to 494 (6.7;490)]	34 (10-268)	n.a.
FIGO stage ^d				
I	9/12 (75.0)	4/6 (66.6)	5 (100)	0
III	3/12 (25.0)	2/6 (33.3)	0	1
Cases contributed per center				
Milan (IEO)	4 (30.7)	3 (42.8)	1 (20)	0
Prague	1 (7.6)	1 (14.2)	0	0
Stockholm	2 (15.3)	1 (14.2)	1(20)	0
Leuven	1 (7.6)	0	0	1
Rome (FPG)	3 (23.07)	1 (14.2)	2 (40)	0
Amsterdam	1 (7.6)	0	1(20)	0
Paris	1 (7.6)	1 (14.2)	0	0

Results are presented as n (%) or median, [range, and interquartile range (IQR)]. ^aInformation available in 6 cases. ^bInformation available in 8 cases.

^cInformation available in 10 cases. ^d Information presented for 12/13, because one tumor was a recurrence.

n.a., not available; IEO, European Institute of Oncology; FPG, Fondazione Policlinico Gemelli.

Normal value of CA 125 is <35 U/mL, normal value of LDH is <250 U/L, normal value of beta-hCG is less than 5 mU/mL, and normal value of AFP is less than 10 ng/mL.

Table 2. Ultrasound characteristics of ovarian malignant mixed germ cell tumor, non-gestational ovarian choriocarcinoma and embryonal ovarian carcinoma.

Characteristic	All n=13	Malignant mixed germ cell tumor n=7	Non-gestational choriocarcinoma n=5	Embryonal carcinoma n=1
Unilateral tumor	13 (100)	7 (100)	5 (100)	1
Ascites	3 (23.1)	3 (42.8)	0	0
Free fluid in the pouch of Douglas	4 (30.7)	3 (42.8)	2 (20)	0
Largest diameter of lesion, mm	129 [38 to 216 (90.5;168)]	129 [51 to 190] (90;180)]	102 [38 to 156 (64.5;150)]	216
Type of tumor				
Multilocular-solid	2 (15.3)	2 (28.5)	0	0
Solid	11 (84.6)	5 (71.5)	5 (100)	1
Number of locules in multilocular-solid masses 4-10	2/2 (100)	2/2 (100)	n.a.	n.a.
Echogenicity of cyst fluid in tumors not classified as solid				
Anechoic	1/2 (50)	1/1	n.a.	n.a.
Mixed	1/2 (50)	1/1	n.a.	n.a.
Largest solid component, mm	91 [15 to 216 (62;150)]	76 [15 to 190 (51;129)]	91 [34 to 156 (60.5;150)]	216
Presence of papillary projection(s)	2 (15.3)	2 (28.5)	0	0
Number of papillary projections if present				
1	1/2 (50)	1	n.a.	n.a.
>3	1/2 (50)	1	n.a.	n.a.
Height of largest papillary projection (mm)	15.5 (14-17)	15.5 (14-17)	n.a.	n.a.
Papillation flow if papillations were present	1/2 (50)	1/2 (50)	n.a.	n.a.
Color score				
1	1 (7.6)	1 (14.2)	0	0
2	0	0	0	0
3	3 (23.07)	2 (28.5)	1 (20)	0
4	9 (69.2)	4 (57.1)	4 (80)	1
Diagnosis on the basis of subjective assessment				
Benign	0	0	0	0
Malignant	9/13(69.2)	7	2	0
Uncertain	4/13 (30.7)	0	3	1
Specific diagnosis suggested by original ultrasound examiner using subjective assessment				
Borderline malignant tumour	1 (7.6)	1 (14.2)	0	0
Primary ovarian cancer	1 (7.6)	1 (14.2)	0	0
Malignant rare stroma cell tumor	1 (7.6)	1 (14.2)	0	0
Malignant rare germ cell tumor	6 (46.1)	4 (57.1)	2 (20)	0

No specific diagnosis suggested

4 (30.7)

0

3 (60)

1

n.a.; not applicable

Results are presented as n (%) or median, [range, and interquartile range (IQR)].

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a

b