Imaging in gynecological disease: clinical and ultrasound characteristics of endometrioid ovarian cancer

[1]Moro F, [1]Magoga G, [1]Pasciuto T, [2]Mascilini F, [2,3]Moruzzi MC, [3]Fischerova D, [4]Savelli L, [4]Giunchi S, [5]Mancari R, [5]Franchi D, [6]Czekierdowski A, [7]Froyman W, [8]Verri D, [9]Epstein E, [10]Chiappa V, [11]Guerriero S, [12]Zannoni GF, [7]Timmerman D, [1]Scambia G, [13]Valentin L, [1]Testa AC

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Running title

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Abstract

Objective To describe the clinical and ultrasound characteristics of ovarian pure endometrioid carcinoma.

Methods This is a retrospective multicenter study. From the International Ovarian Tumor Analysis (IOTA) database we identified 161 patients with a histological diagnosis of pure endometrioid carcinoma, who had undergone preoperative ultrasound examination by an experienced ultrasound examiner between 1999 and 2016. Another 78 patients with a histological diagnosis of pure endometrioid carcinoma were identified from the databases of the departments of gynecological oncology in the participating centers. All tumors were

described using IOTA terminology. In addition, one author reviewed all available ultrasound images and described them using pattern recognition.

Results Median age of the 239 patients was 55 (range, 19-88) years. On ultrasound examination, two (0.8%) endometrioid carcinomas were described as unilocular cysts, three (1.3%) as multilocular cysts, 37 (15.5%) as unilocular-solid cysts, 115 (48.1%) as multilocular-solid cysts and 82 (34.3%) as solid masses. The largest tumor diameter was median 102.5 (range 20-300) mm and the largest diameter of the largest solid component was median 63 (range 9-300) mm. Papillary projections were present in 70 (29.3%) masses. Most cancers (188, 78.7%) were unilateral. In 49 (20.5%) cases, the cancer was judged by the pathologist to arise in endometriosis. These cancers more often manifested papillary projections on ultrasound than those without evidence of tumor arising in endometriosis (46.9% vs 24.7%; 23/49 vs 47/190), were less often bilateral (8.2% vs 24.7%; 4/49 vs 47/190) and less often associated with ascites (6.1% vs 28.4%; 3/49 vs 54/190) and fluid in the pouch of Douglas (24.5% vs 48.9%; 12/49 vs 93/190). Retrospective analysis of available ultrasound images using pattern recognition revealed that many tumors without evidence of tumor arising in endometriosis (36.3%; 41/113) had a large central solid component entrapped within locules giving the tumor a cockade-like appearance.

Conclusions Endometrioid cancers are usually large, unilateral, multilocular-solid or solid tumors. The ultrasound characteristics of endometrioid carcinomas arising in endometriosis differ from those without evidence of tumor arising in endometriosis, cancers arising in endometriomas more often being unilateral cysts with papillary projections and no ascites.

Introduction

Aim

The aim of this study is to describe the clinical and ultrasound characteristics of pure endometrioid ovarian carcinoma

Background

Epidemiology

Endometrioid carcinoma accounts for 10-15% of ovarian epithelial carcinomas, representing the second most common type of ovarian epithelial cancer.[1] This tumor is most often diagnosed in the fifth and sixth decades and the mean age at presentation is 55-58 years, i.e. slightly lower than that for the most common epithelial cancer, serous carcinoma.[2]

A substantial proportion (10-50%) of ovarian endometrioid carcinomas arise in endometriosis.[3] The association between endometriosis and ovarian cancer was first described by Sampson in 1925.[4] He developed strict criteria to define malignant transformation of endometriosis: endometriosis close to the tumor; malignant foci arising in endometrioid lesions rather than originating outside these lesions; and the presence of tissue resembling endometrial stroma surrounding the characteristic glands. Scott added a fourth criterion:[5] histologically proven transition from benign endometriosis to cancer. However, Fukunaga et al, in a case series of 224 malignant epithelial tumors, found that 54 of them manifested evidence of tumor arising in endometriosis according to Sampson and/or Scott

criteria, but only 13/54 (24%) showed a true transitional area from endometriosis to a malignant epithelial tumor.[6]

It has been reported that 15-20% of endometrioid carcinomas in the ovary coexist with endometrial carcinoma.[1] In these cases, usually both the ovarian and endometrial tumors are well differentiated and resemble each other. The criteria for distinguishing metastatic from independent primary ovarian carcinomas rely mainly on clinico-pathological findings. In cases of low-grade endometrial carcinoma associated with hyperplasia and minimal or no myometrial invasion, the ovarian tumor can be regarded as an independent primary tumor, particularly if endometriosis is also present. Bilaterality, multinodular growth, vascular space invasion and tubal invasion, are characteristics of ovarian metastases of endometrial cancer.[1]

According to the dualistic model of epithelial ovarian carcinogenesis,[7] endometrioid carcinoma is a Type I tumor. Type I tumors appear to develop from well-established precursor lesions (such as endometriosis for endometrioid and clear cell carcinomas). These may undergo malignant transformation in a slow step-wise fashion. In contrast, Type II tumors (i.e. high grade serous carcinomas) develop from intraepithelial carcinomas in the fallopian tube that disseminate into the ovary and extra-ovarian sites and have an aggressive behaviour.

Microscopy

Endometrioid adenocarcinoma is classically characterized by confluent glandular epithelial proliferation exceeding the limit for microinvasion (5 mm). This pattern is typically characterized by extensive glandular branching, budding, true cribriform architecture, and highly complex papillary proliferations. Less frequently, a destructive infiltrative pattern is seen.[1]

Most ovarian endometrioid carcinomas are well differentiated and show low-grade nuclei (i.e. grade 1 and grade 2 nuclei). Poorly differentiated endometrioid carcinomas are predominantly solid with focal microglandular areas. The grade of endometrioid carcinoma is determined by the microscopic appearance of the tumor. It is based on both the architectural pattern and the nuclear features.[1] The architectural grade is determined by the extent to which the tumor is composed of solid masses of cells as compared with well-defined glands: grade 1 when no more than 5% of the tumor is composed of solid masses, grade 2 when 6-50% of the tumor is composed of solid masses and grade 3 when more than 50% of the tumor is composed of solid masses. The nuclear grade is determined by nuclear size and shape, chromatin distribution, and size of the nucleoli. Grade 1 nuclei are oval, mildly enlarged, and have evenly dispersed chromatin; grade 3 nuclei are markedly enlarged and pleomorphic, with irregular coarse chromatin, and prominent eosinophilic nucleoli. Grade 2 nuclei have features intermediate between grades 1 and 3.

The microscopic features described above are typical of pure endometrioid carcinoma, which is the most common variant of endometrioid ovarian carinoma.[1] Other variants exist, e.g. endometrioid carcinoma with squamous differentiation (characterized by squamous cells), sertoliform endometrioid carcinomas, endometrioid carcinomas resembling sex cord-stromal tumor, endometroid carcinoma with an undifferentiated neuroendocrine component, and endometrioid carcinoma mixed with clear cell carcinoma.[1,8]

Macroscopy

Endometrioid carcinomas have a mean size of 15 cm and have a smooth outer surface. They are unilateral in 83-87% of cases.[1,8] The cut surface can display friable soft masses or papillae partly filling cystic spaces that contain blood-stained fluid[1]. They can also be completely solid, exhibiting hemorrhage or necrosis. Tumors arising in endometriosis may

display gross findings of an endometriotic cyst containing chocolate-colored fluid with one or more solid nodules or papillary excrescences protruding from the wall.[1]

Clinical features and prognosis

The most common symptoms are pelvic pain and abdominal distension, but abnormal vaginal bleeding is also frequent because of the association of ovarian endometrioid carcinoma with endometrial hyperplasia with atypia and endometrial carcinoma.[1] Serum CA125 is elevated in more than 80% of cases.[1] The stage distribution of endometrioid carcinomas differs from that of both low-grade and high-grade serous carcinoma. Most patients with a low-grade or high-grade serous carcinoma present at an advanced stage (III-IV),[9] whereas approximately 80% of ovarian endometrioid carcinomas present with disease confined to the pelvis (stage I and II).[10,11] Endometrioid carcinoma carries the most favorable prognosis of all ovarian carcinoma histotypes with a 5-year survival rate of more than 70% if one does not take stage into account. For patients diagnosed at stage IA/IB/IC1 (IC1 meaning surgical spill only) according to FIGO (International Federation of Obstetricians and Gynecologists) 2014,[12] the 5-year survival is about 95%, and those patients do not require adjuvant therapy after surgery.[11,13]

Methods

This is a retrospective multicenter study. From the International Ovarian Tumor Analysis (IOTA) database we identified patients with a histological diagnosis of pure endometrioid carcinoma, who had undergone preoperative ultrasound examination by an experienced ultrasound examiner between 1999 and 2016 (IOTA phase 1, 1b, 2, 3 and 5).[14-17] Additional patients with a histological diagnosis of pure endometrioid carcinoma and with available ultrasound images who had been investigated outside the IOTA protocol between 2007 and

2016 were retrospectively identified from databases of the departments of gynecological oncology of the participating centers. Eleven ultrasound centers contributed patients to the study (Table 1 and Supplementary Table S1).

All patients had been preoperatively examined with transvaginal ultrasound (supplemented with a transabdominal scan, if necessary) using a standardized examination technique.[18] 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 study protocol, 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. Final histology, tumor grade, FIGO stage,[12] presence of a synchronous endometrial cancer, and signs of cancer arising in endometriosis as judged by the local pathologist were 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.[18] Papillary projections were defined as projections of solid tissue into the cystic cavity arising from the cyst wall or from a septum with a height greater than or equal to 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.[18] The presence of ascites and fluid in the pouch of Douglas was noted. The vascularization of the tumors on color 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 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, one author with more than 10 years' experience in gynecological ultrasound (F.M.), assessed available ultrasound images (most of them electronic) of pure ovarian endometrioid carcinomas using pattern recognition[19] with the aim to identify typical ultrasound patterns. Doing so F.M. was blinded to the histological findings (tumor arising in endometriosis or not, presence of a synchronous endometrial cancer or not).

All clinical and ultrasound data were entered into a dedicated Excel file (Microsoft Office Excel 2007, Redmond, WA, USA). Results are presented as absolute frequency (percentage) for nominal variables and as median (range) for continuous variables. Mann-Whitney test for continuous variables and $\chi 2$ or Fisher's exact test for nominal variables were used as appropriate. All the statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS Statistic, IBM corp., New York, NY, USA, PASW version 20.0). Two-sided tests were used and the significance level was set at $P < 0.05$.

Results

We identified 161 patients with pure endometrioid cancer from the IOTA databases and another 78 patients examined outside the IOTA studies. There were no substantial differences either in clinical or ultrasound characteristics between cases examined inside or outside the IOTA studies (Supplementary Table S1 and S2), and so results are presented for all 239 cases

together. Demographic background data and tumor characteristics of all patients are shown in Table 1. Median age was 55 (range, 19-88) years and 93/239 (38.9%) patients were premenopausal. Most tumors were FIGO Stage I (139/238, 58.4%) and most were well-differentiated (grade 1 or 2 in 155/219, 70.8%). The sonographic characteristics of the endometrioid carcinomas are shown in Table 2. Most tumors (188, 78.7%) were unilateral. The median largest diameter was 102.5 (range 20-300) mm. Almost all endometrioid carcinomas were described as unilocular-solid (37, 15.5%), multilocular-solid (115, 48.1%) or solid masses (82, 34.3%) and the median largest diameter of the largest solid component was 63 (range 9-300) mm. Papillary projections were seen in 70 (29.3%) masses and most of the masses with papillary projections contained more than three papillary projections, the median height of the largest papillary projection being 16 (range, 4-64) mm. The most common echogenicity of cyst fluid was low level echogenicity (83/157, 52.9%). Ground glass echogenicity was uncommon (25/157, 15.9%). All but three tumors were vascularized at color Doppler examination, and most had color score 3 or 4 (186/238, 78.2%). On the basis of subjective assessment by the original ultrasound examiner, 202 (84.5%) masses were classified as malignant, 27 (11.3%) as borderline tumors and ten (4.2%) as benign tumors. Four of the ten tumors misdiagnosed as benign masses were suspected to be fibromas/fibrothecomas, two to be endometriomas, two to be hydrosalpinx/pelvic inflammatory disease, one to be a cystadenoma and one to be a dermoid cyst. Ultrasound images are available for eight of the ten misclassified cancers and these are shown in Supplementary Figure S1.

In 49/239 (20.5%) patients the pathologist judged the cancer to arise in endometriosis, and 11 (22.4%) of these patients also had a synchronous endometrial cancer, while information on synchronous endometrial cancer was lacking in three of them. Of the 190 patients with a tumor with no evidence of the cancer arising in endometriosis, 30 (15.8%) also had a

synchronous endometrial cancer, while information on synchronous endometrial cancer was lacking in 11 of them.

Patients with cancer arising in endometriosis had lower serum CA 125 levels than those with no evidence of cancer arising in endometriosis (median 64 U/mL vs 256.5 U/mL) and the cancers arising in endometriosis were more often stage I (81.6% vs 52.4%; 40/49 vs 99/189) and grade 1 (34.7% vs 23.5%; 17/49 vs 40/170) (Table 1). Ultrasound characteristics of endometrioid cancers arising in endometriosis and of those with no evidence of cancer arising in endometriosis are shown in Table 2 and in Figures 1 and 2. Endometroid cancers arising in endometriosis were more often unilateral than those not arising in endometriosis (91.8% vs 75.3%; 45/49 vs 143/190), they were less often associated with ascites (6.1% vs 28.4%, 3/49 vs 54/190) and free fluid in the pouch of Douglas (24.5% vs 48.9%; 12/49 vs 93/190), and if they were multilocular or multilocular-solid they contained fewer cyst locules (two or three cyst locules 46.4% vs 18.9%; 13/28 vs 17/90). They were more often unilocular-solid tumors (28.6% vs 12.1%; 14/49 vs 23/190) and less often solid tumors (12.2% vs 40.0%; 6/49 vs 76/190), and they more often contained papillary projections (46.9% vs 24.7%; 23/49 vs 47/190) than endometrioid cancers with no evidence of tumor arising in endometriosis.

The small sample sizes preclude a reliable estimation of any differences in clinical background data or ultrasound features between endometroid cancers arising in endometriosis with and without a synchronous endometrial cancer, and between endometroid cancers not arising in endometriosis with and without a synchronous endometrial cancer (Supplementary Table S3 and S4 and in Supplementary Figure S2). No obvious differences in ultrasound appearance were seen. However, patients with endometroid ovarian cancers not arising in endometriosis with a synchronous endometrial cancer were younger and more often nulliparous than those without a synchronous endometrial cancer. CA125 values seemed to

be lowest in women with cancer arising in endometriosis without a synchronous endometrial cancer.

Ultrasound images were available for 66 of the 161pure ovarian endometrioid carcinomas in the IOTA database and for all 78 patients examined outside the IOTA studies, i.e. for 144/239 (60%) of the endometrioid cancers. On retrospective review of these, 17/31 (54.8%) endometrioid cancers arising in endometriosis were described by the reviewer of the images as cysts with papillary projections (Figure 1). The most typical ultrasound image (41/113, 36.3%) of an endometrioid cancer not arising in endometriosis was a cyst with a large central solid component entrapped within locules. This gave the lesion a cockade-like appearance (Figure 2). Using pattern recognition, no obvious differences were found between cancers arising in endometriosis with and without synchronous endometrial cancer and no obvious differences were found between cancers not arising in endometriosis with and without synchronous endometrial cancer (Supplementary Figure S2).

Discussion

In this study we have described the clinical and ultrasound characteristics of pure endometrioid ovarian carcinomas. The median age at the diagnosis was 55 (range 19-88) years and most tumors were FIGO stage I and grade 1 or 2. On ultrasound, most endometroid cancers were large, unilateral, multilocular-solid tumors, usually with low level echogenicity of cyst fluid, or solid masses. About 20% of the endometrioid cancers arose in endometriosis and approximately 20% were associated with a synchronous endometrial cancer. When using pattern recognition cancers arising in endometriosis were often described as cysts with papillary projections, while carcinomas without evidence of tumor arising in endometriosis

were often described as tumors with a large central solid component entrapped within locules giving the tumor a cockade-like appearance.

The strength of our study is that it is a large series of pure ovarian endometrioid carcinoma described in a standardized manner. Our study also has limitations. First, it is retrospective. This means that some clinical and histological information was sometimes missing. Second, we cannot guarantee that all pathologists strictly applied Sampson´s criteria for cancer arising in endometriosis. Third, ultrasound images or video clips were not available for all cases, and this may have limited our possibility to detect typical ultrasound features.

Our clinical findings agree with those of others[20] in that endometrioid cancers with evidence of tumor arising in endometriosis more often were diagnosed at an early stage and more often were Grade 1 or 2 than those with no evidence of tumor arising in endometriosis. We have found no direct support in the literature for our finding that patients with endometrioid cancer not arising in endometriosis with synchronous endometrial cancer were substantially younger and more often nulliparous than the patients with endometrioid cancer not arising in endometriosis without synchronous endometrial cancer. Indirect support is that Uccella et al reported patients with endometrial cancer and a synchronous ovarian cancer to be younger than those with endometrial cancer without a synchronous ovarian cancer.[21] Our results harmonize with the macroscopic features of endometrioid cancers reported in textbooks of pathology, in which they are described as unilateral and quite large solid tumors or cysts with solid masses or papillations, and in which endometrioid cancers arising in endometriotic cysts are described as cysts with one or more papillary excrescences protruding from the internal cyst wall.[8] They also agree with those of Testa et al who reported that the typical ultrasound appearance of an ovarian cancer arising in endometriosis is a cyst with papillary projections.[22] However, not all cancers in the series of Testa et al were endometrioid cancers, some were clear cell cancers and one was a borderline tumor of mucinous

endocervical type. In contrast to endometriomas with endometrioid or other epithelial malignancy arising in them, benign ovarian endometriomas typically appear as unilocular or multilocular cyst without solid components, even though their ultrasound appearance may vary slightly with age.[23, 24] In a large series of malignant ovarian tumors including invasive epithelial ovarian cancers of all histotypes, Valentin and co-authors[25] found a higher proportion of masses with papillations (67% of epithelial ovarian cancers at stage I and 41% of epithelial ovarian cancers at stage II-IV) than we did in our series (29.3%) which includes only endometrioid ovarian tumors. The cockade like appearance of endometrioid cancer has not been described by others. It remains to be shown, if this is indeed a specific sign of endometrioid cancer, or if it is also found in other primary epithelial ovarian cancers.

The original ultrasound examiner correctly classified the vast majority of endometrioid ovarian cancers (202/239, 84.5%) as invasive malignant tumors. Only 10/239 (4.2%) were misdiagnosed as benign. This confirms the high accuracy of ultrasound for discriminating between benign and malignant ovarian masses.[26-27] However, 27/239 (11.3%) endometrioid cancers were misdiagnosed as borderline tumors. This is likely to be explained by many endometrioid cancers having papillary projections, which are common in serous borderline tumors and in mucinous endocervical-type borderline tumors.[28,29]

The ultrasound characteristics of endometrioid ovarian cancers differ from those of mucinous and serous ovarian carcinomas previously described[29,30] (Supplementary Table S5). Whether it is possible to discriminate correctly between different types of ovarian malignancies on the basis of ultrasound images and clinical information can only be determined in a prospective study. However, before starting any prospective study, the typical ultrasound appearance of different types of ovarian malignancy must be known. The typical ultrasound appearance of several different adnexal pathologies, including various types of malignancy, has been described in the “imaging in gynecological disease” series of this journal. [29-38]

To preoperatively distinguish an endometrioid carcinoma from other invasive tumors has some clinical importance because of the favorable prognosis of these tumors, especially those arising in endometriotic cysts. Suspicion of endometrioid cancer and of endometrioid cancer arising in an endometrioma may affect preoperative counselling. For example, optimal cytoreduction is likely to be achievable in patients with endometrioid carcinoma because endometrioid cancers are often diagnosed at low stage.[7] Moreover, in patients who want to preserve their fertility, conservative surgery might be possible for a stage I endometrioid cancer arising in an endometriotic cyst, because these tumors seem to have a better prognosis than those not arising in endometriosis.[39]

References

1. Longacre TA, Wells M. Endometrioid Tumors. In Blaustein's Pathology of the Female Genital Tract. Kurman RJ, Hedrick Ellenson L, Ronnet BM (eds). *Springer New York Dodrecht Heidelberg London*, 2011; 748–758.

2. Storey DJ, Rush R, Stewart M, Rye T, Al-Nafussi A, Williams AR, Smyth JF, Gabra H. Endometrioid epithelial ovarian cancer: 20 years of prospectively collected data from a single center. *Cancer* 2008; **15** : 2211–2220.

3. Davis M, Rauh-Hain JA, Andrade C, Boruta DM 2nd, Schorge JO, Horowitz NS, May T, del Carmen MG. Comparison of clinical outcomes of patients with clear cell and endometrioid ovarian cancer associated with

endometriosis to papillary serous carcinoma of the ovary. *Gynecol Oncol* 2014; **132** : 760-766.

4. Sampson JA. Endometrial carcinoma of the ovary, arising in endometrial tissue in that organ. *Ann Surg* 1925; **10** : 1–72.

5. Scott RB. Malignant changes in endometriosis. *Obstet Gynecol* 1953; **2**: 283 – 289.

6. Fukunaga M, Nomura K, Ishikawa E, Ushigome S. Ovarian atypical endometriosis: its close association with malignant epithelial tumors. *Histopathology* 1997; **30**: 249 – 255.

7. Kurman RJ, Shih IeM. The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. *Am J Pathol* 2016; **186** : 733–747.

8. Longacre TA, Wells M. Endometrioid tumours. In *WHO Classification of Tumours of Female Reproductive Organs*, Kurman RJ, Carcangiu ML, Herrington CS, Young RH (eds). *IARC Lyon*, 2014; 29–32.

9. Angarita AM, Cholakian D, Fader AN. Low-grade serous carcinoma: molecular features and contemporary treatment strategies. *Expert Rev Anticancer Ther* 2015;**15** : 893–899.

10. Köbel M, Kalloger SE, Huntsman DG, Santos JL, Swenerton KD, Seidman JD, Gilks CB. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. *Int. J. Gynecol. Pathol* 2010; **29** : 203–211.

11. Rambau P, Kelemen LE, Steed H, Quan ML, Ghatage P, Köbel M. Association of Hormone Receptor Expression with Survival in Ovarian Endometrioid Carcinoma: Biological Validation and Clinical Implications. *Int J Mol Sci* 2017; **27** : 18(3).

12. Kandukuri SR, Rao J. FIGO 2013 staging system for ovarian cancer: what is new in comparison to the 1988 staging system? *Curr Opin Obstet Gynecol* 2015; **27** : 48–52

13. Köbel M, Kalloger SE, Lee S, Duggan MA, Kelemen LE, Prentice L, Kalli KR, Fridley BL, Visscher DW, Keeney GL, Vierkant RA, Cunningham JM, Chow C, Ness RB, Moysich K, Edwards R, Modugno F, Bunker C, Wozniak EL, Benjamin E, Gayther SA,Gentry-Maharaj A, Menon U, Gilks CB, Huntsman DG, Ramus SJ, Goode EL; OvarianTumor Tissue Analysis consortium.Biomarker-based ovarian carcinoma typing: A histologic investigation in the ovarian tumor tissue analysis consortium. *Cancer Epidemiol. Biomark. Prev* 2013, **22** : 1677–1686.

14. Timmerman D, Testa AC, Bourne T, Ferrazzi E, Ameye L, Konstantinovic ML, Valentin L. Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International Ovarian Tumor Analysis Group. *J Clin Oncol* 2005; **23**: 8794–8801.

15. Timmerman D, Van Calster B, Testa AC, Guerriero S, Fischerova D, Lissoni AA, Van Holsbeke C, Fruscio R, Czekierdowski A, Jurkovic D, Savelli L, Vergote I, Bourne T, Van Huffel S, Valentin L. Ovarian cancer prediction in adnexal masses using ultrasound-based logistic regression models: a temporal and external validation study by the IOTA group. *Ultrasound Obstet Gynecol* 2010; **36** : 226–234.

16. Van Holsbeke C, Van Calster B, Testa AC, Domali E, Lu C, Van Huffel S, Valentin L, Timmerman D. Prospective internal validation of mathematical models to predict malignancy in adnexal masses: results from international ovarian tumor analysis study. *Clin Cancer Res* 2009; **15** : 684–681.

17. Testa A, Kaijser J, Wynants L, Fischerova D, Van Holsbeke C, Franchi D, Savelli L, Epstein E, Czekierdowski A, Guerriero S, Timmerman D. Strategies to diagnose ovarian cancer: New evidence from phase 3 of the multicentre international IOTA study. *Br J Cancer* 2014; **111** : 680–688.

18. Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. *Ultrasound Obstet Gynecol* 2000; **16**: 500–505.

19. Valentin L. Pattern recognition of pelvic masses by gray-scale ultrasound imaging: the contribution of Doppler ultrasound. *Ultrasound Obstet Gynecol* 1999; **14** : 338–347.

20. Mangili G, Bergamini A, Taccagni G, Gentile C, Panina P, Viganò P, Candiani M. Unraveling the two entities of endometrioid ovarian cancer: A single center clinical experience. *Gynecol Oncology* 2012; **126** : 403–407.

21. Uccella S, Cha SS, Melton LJ 3rd, Bergstralh EJ, Boardman LA, Keeney GL, Podratz KC, Ciancio FF, Mariani A. Risk factors for developing multiple malignancies in patients with endometrial cancer. *Int J Gynecol Cancer* 2011; **21** : 896–901.

22. Testa AC, Timmerman D, Van Holsbeke C, Zannoni GF, Fransis S, Moerman P, Vellone V, Mascilini F, Licameli A, Ludovisi M, Di Legge A, Scambia G, Ferrandina G. Ovarian cancer arising in endometrioid cysts: ultrasound findings. *Ultrasound Obstet Gynecol* 2011; **38** : 99–106.

23. Van Holsbeke C, Van Calster B, Guerriero S, Savelli L, Paladini D, Lissoni AA, Czekierdowski A, Fischerova D, Zhang J, Mestdagh G, Testa AC,

Bourne T, Valentin L, Timmerman D. Endometriomas: their ultrasound characteristics. *Ultrasound Obstet Gynecol* 2010; **35** : 730-40.

24. Guerriero S, Van Calster B, Somigliana E, Ajossa S, Froyman W, De Cock B, Coosemans A, Fischerová D, Van Holsbeke C, Alcazar JL, Testa AC, Valentin L, Bourne T, Timmerman D. Age-related differences in the sonographic characteristics of endometriomas. *Hum Reprod* 2016; **31** : 1723–1731.

25. Valentin L, Ameye L, Testa A, Lécuru F, Bernard JP, Paladini D, Van Huffel S, Timmerman D. Ultrasound characteristics of different types of adnexal malignancies. *Gynecol Oncol* 2006; **102** : 41–48.

26. Valentin L, Hagen B, Tingulstad S, Eik-Nes S. Comparison of 'pattern recognition' and logistic regression models for discrimination between benign and malignant pelvic masses: a prospective cross validation. *Ultrasound Obstet Gynecol* 2001; **18** : 357-365.

27. Timmerman D. The use of mathematical models to evaluate pelvic masses; can they beat an expert operator? *Best Pract Res Clin Obstet Gynaecol* 2004; **18** : 91-104. Review.

28. Fruscella E, Testa AC, Ferrandina G, De Smet F, Van Holsbeke C, Scambia G, Zannoni GF, Ludovisi M, Achten R, Amant F, Vergote I, Timmerman D. Ultrasound features of different histopathological subtypes of borderline ovarian tumors. *Ultrasound Obstet Gynecol* 2005; **26** : 644–650.

29. Moro F, Baima Poma C, Zannoni GF, Vidal Urbinati A, Pasciuto T, Ludovisi M, Moruzzi MC, Carinelli S, Franchi D, Scambia G, Testa AC. Imaging in gynecological disease (12): clinical and ultrasound features of invasive and non-invasive malignant serous ovarian tumors. *Ultrasound, Obstet Gynecol* 2017; 50 : 788–799.

30. Moro F, Zannoni GF, Arciuolo D, Pasciuto T, Amoroso S, Mascilini F, Mainenti S, Scambia G, Testa AC. Imaging in gynecological disease (11): clinical and ultrasound features of mucinous ovarian tumors. *Ultrasound Obstet Gynecol* 2017; 50 : 261–270.

31. Testa AC, Ferrandina G, Timmerman D, Savelli L, Ludovisi M, Van Holsbeke C, Malaggese M, Scambia G, Valentin L. Imaging in Gynecological Disease (1): Ultrasound Features of Metastases in the Ovaries Differ Depending on the Origin of the Primary Tumor. *Ultrasound Obstet Gynecol* 2007; 29 : 505–511.

32. Demidov VN, Lipatenkova J, Vikhareva O, Van Holsbeke C, Timmerman D, Valentin L. Imaging of gynecological disease (2): clinical and ultrasound characteristics of Sertoli cell tumors, Sertoli-Leydig cell tumors and Leydig cell tumors. Ultrasound Obstet Gynecol 2008; **31** : 85-91.

33. Van Holsbeke C, Domali E, Holland TK, Achten R, Testa AC, Valentin L, Jurkovic D, Moerman P, Timmerman D. Imaging of gynecological disease (3): clinical and ultrasound characteristics of granulosa cell tumors of the ovary. Ultrasound Obstet Gynecol 2008; **31** : 450-456.

34. Savelli L, Testa AC, Timmerman D, Paladini D, Ljungberg O, Valentin L. Imaging of gynecological disease (4): clinical and ultrasound characteristics of struma ovarii. Ultrasound Obstet Gynecol. 2008; **32** : 210-219.

35. Guerriero S, Testa AC, Timmerman D, Van Holsbeke C, Ajossa S, Fischerova D, Franchi D, Leone FP, Domali E, Alcazar JL, Parodo G, Mascilini F, Virgilio B, Demidov VN, Lipatenkova J, Valentin L. Imaging of gynecological disease (6): clinical and ultrasound characteristics of ovarian dysgerminoma. Ultrasound Obstet Gynecol 2011; **37** : 596-602.

36. Dierickx I, Valentin L, Van Holsbeke C, Jacomen G, Lissoni AA, Licameli A, Testa A, Bourne T, Timmerman D. Imaging in gynecological disease (7): clinical and ultrasound features of Brenner tumors of the ovary. Ultrasound Obstet Gynecol 2012; 40 : 706-713.

37. Franchi D, Boveri S, Fruscio R, Fischerova D, Guerriero S, Moruzzi MC, Colombo N, Timmerman D, Valentin L, Testa AC. Imaging in gynecological disease (8): ultrasound characteristics of recurrent borderline ovarian tumors. Ultrasound Obstet Gynecol 2013; **41** : 452-458.

38. Ludovisi M, De Blasis I, Virgilio B, Fischerova D, Franchi D, Pascual MA, Savelli L, Epstein E, Van Holsbeke C, Guerriero S, Czekierdowski A, Zannoni G, Scambia G, Jurkovic D, Rossi A, Timmerman D, Valentin L, Testa AC. Imaging in gynecological disease (9): clinical and ultrasound characteristics of tubal cancer. *Ultrasound Obstet Gynecol* 2014; **43** : 328-335.

39. Kumar S, Munkarah A, Arabi H, Bandyopadhyay S, Semaan A, Hayek K, Garg G, Morris R, Ali-Fehmi R. Prognostic analysis of ovarian cancer associated with endometriosis. *Am J Obstet Gynecol* 2011; **204** : 63.e1–7.

Figure legends

Figure 1 Ultrasound images of pure endometrioid carcinomas arising in endometriosis on histological examination. Most were described as unilocular-solid masses (a,b,c,d,e,f) or multilocular-solid masses (g,h,i). Papillary projections were seen in 23/49 (46.9%) masses (a,b,c,d,e,f,g,h).

Figure 2 Ultrasound images of pure endometrioid carcinomas without evidence of tumor arising in endometriosis on histological examination. Most were described as multilocular-solid masses (a,b,c,d,e,f,g) or solid masses (h,i). Cockade like appearance is seen in (a,b,c,d,e,f,g).

Supplementary Figure S1 Ultrasound images of eight endometrioid carcinomas misdiagnosed as benign masses by the original examiner. One mass was misdiagnosed as a dermoid cyst (a), one as a cystadenoma (b), one as pelvic inflammatory disease (c), one as hydrosalpinx (d), two as endometriomas (e, f) and two as fibromas (g, h).

Supplementary Figure S2 Ultrasound images of endometrioid carcinoma arising in endometriosis with synchronous endometrial cancer (a), endometrioid carcinoma arising in endometriosis without synchronous endometrial cancer (b), endometrioid carcinoma not arising in endometriosis and synchronous endometrial cancer (c) endometrioid carcinoma not arising in endometriosis with no synchronous endometrial cancer (d).

Table 1 Clinical and tumor characteristics for patients with pure endometrioid ovarian cancer with versus without evidence of it arising in endometriosis

Characteristic	All n=239	Cancer arising in endometriosis n= 49	Cancer with no evidence of the tumor arising in endometriosis n= 190	P-value
Age at diagnosis (years)	55 (19-88)	53 (26-86)	55 (19-88)	0.094
Nulliparous [a]	56/172 (32.6)	19/39 (48.7)	37/133 (27.8)	0.014
Current hormonal therapy [b]	12/236 (5.1)	6/49 (12.2)	6/187 (3.2)	0.021
Premenopausal	93 (38.9)	22 (44.9)	71 (37.4)	0.335
Previous surgical treatment				
Hysterectomy	14 (5.9)	4 (8.2)	10 (5.3)	0.441
Unilateral oophorectomy [c]	12/231 (5.2)	3/47 (6.4)	9/184 (4.9)	0.713
CA125 serum levels at diagnosis [d] (U/mL)	179 (7-57900)	64 (7-3174)	256.5 (7-57900)	<0.0001
FIGO stage [e]				0.001

I	139/238 (58.4)	40 (81.6)	99 (52.4)	
II	18/238 (7.6)	4 (8.2)	14 (7.4)	
III	75/238 (31.5)	5 (10.2)	70 (37.0)	
IV	6/238 (2.5)	0 (0)	6 (3.2)	
Grade [f]				0.027
1	57/219 (26.1)	17/49 (34.7)	40/170 (23.5)	
2	98/219 (44.7)	25/49 (51.0)	73/170 (42.9)	
3	64/219 (29.2)	7/49 (14.3)	57/170 (33.6)	
Synchronous endometrial tumor present [g]	41/225 (18.2)	11/46 (23.9)	30/179 (16.8)	0.286
Cases contributed per centers				-
Cagliari	2 (0.8)	1 (2.0)	1 (0.5)	
Milan (NCI)	6 (2.5)	2 (4.1)	4 (2.1)	
Stokholm	9 (3.8)	1 (2.0)	8 (4.2)	
Monza	11 (4.6)	1 (2.0)	10 (5.3)	
Malmo	12 (5.0)	2 (4.1)	10 (5.3)	
Leuven	17 (7.1)	3 (6.1)	14 (7.4)	
Bologna	23 (9.6)	6 (12.2)	17 (8.9)	
Prague	26 (10.9)	13 (26.6)	13 (6.8)	
Milan (EIO)	31 (13.0)	12 (24.5)	19 (10.0)	
Lublin	34 (14.2)	0 (0)	34 (17.9)	
Rome	68 (28.5)	8 (16.4)	60 (31.6)	

Results are presented as n (%) or median (range). P-values denote the statistical significance of differences between cancers arising in endometriosis and not arising in endometriosis. [a] Information available in 172 cases. [b] Information available in 236 cases. [c] Information available in 231 cases. [d] Information available in 206 cases. [e] Information available in 238 cases. [f] Information available in 219 cases. [g] Information available in 225 cases. NCI: National Cancer Institute. EIO: European Institute of Oncology.

Table 2 Ultrasound characteristics of pure endometrioid ovarian cancer with versus without evidence of it arising in endometriosis

Characteristic	All n=239	Cancer arising in endometriosis n= 49	Cancer with no evidence of the tumor arising in endometriosis n= 190	P-value*
Unilateral tumor	188 (78.7)	45 (91.8)	143 (75.3)	0.011
Ascites	57 (23.8)	3 (6.1)	54 (28.4)	0.001
Free fluid in the pouch of Douglas	105 (43.9)	12 (24.5)	93 (48.9)	0.002
Largest diameter of lesion (mm)	102.5 (20-300)	83 (24-234)	103.5 (20-300)	0.361
Type of tumor				0.002
Unilocular	2 (0.8)	1 (2.0)	1 (0.5)	
Multilocular	3 (1.3)	1 (2.0)	2 (1.1)	
Unilocular-solid	37 (15.5)	14 (28.6)	23 (12.1)	
Multilocular-solid	115 (48.1)	27 (55.1)	88 (46.3)	
Solid	82 (34.3)	6 (12.2)	76 (40.0)	
Number of locules in multilocular and multilocular-solid masses				0.003
2	16 (13.6)	6 (21.4)	10 (11.1)	
3	14 (11.9)	7 (25.0)	7 (7.8)	
4-10	51 (43.2)	13 (46.4)	38 (42.2)	
>10	37 (31.4)	2 (7.1)	35 (38.9)	
Echogenicity of cyst fluid in tumors not classified as solid				0.176
Anechoic	37 (23.5)	5 (11.6)	32 (28.1)	
Low level	83 (52.9)	24 (55.8)	59 (51.8)	
Ground glass	25 (15.9)	10 (23.3)	15 (13.2)	
Haemorragic	2 (1.3)	0 (0)	2 (1.8)	
Mixed	10 (6.4)	4 (9.3)	6 (5.3)	
Largest solid component (mm) [a]	63 (9-300)	45 (9-160)	68 (9-300)	<0.0001
Presence of papillary projection/s	70 (29.3)	23 (46.9)	47 (24.7)	0.002
Number of papillary projections if papillations were present				0.393
1	16 (22.9)	6 (26.1)	10 (21.3)	
2	9 (12.9)	4 (17.4)	5 (10.6)	
3	8 (11.4)	4 (17.4)	4 (8.5)	
>3	37 (52.9)	9 (39.1)	28 (59.6)	
Height of largest papillary projection (mm)	16 (4-64)	15 (5-51)	17.5 (4-64)	0.924
Papillation flow if papillations were present [b]	15/69 (21.7)	2/22 (9.1)	13/47 (27.7)	0.072
Incomplete septa [c]	10/235 (4.3)	1/48 (2.1)	9/187 (4.8)	0.692
Shadowing	15 (6.3)	1 (2.0)	14 (7.4)	0.171
Color score [d]				0.061
1	3/238 (1.3)	0/49 (0)	3/189 (1.6)	
2	49/238 (20.6)	15/49 (30.6)	34/189 (18.0)	
3	113/238 (47.5)	16/49 (32.7)	97/189 (51.3)	
4	73/238 (30.6)	18/49 (36.7)	55/189 (29.1)	
Diagnosis on the basis of subjective assessment				0.144
Benign	10 (4.2)	3 (6.1)	7 (3.7)	
Borderline	27 (11.3)	9 (18.4)	18 (9.5)	
Malignant	202 (84.5)	37 (75.5)	165 (86.8)	
Specific diagnosis suggested by original ultrasound examiner				0.259
Fibroma / fibrothecoma	4 (1.7)	1 (2.0)	3 (1.6)	
Endometriosis	2 (0.8)	0 (0)	2 (1.1)	
Cystadenoma	1 (0.4)	0 (0)	1 (0.5)	
Hydrosalpinx	1 (0.4)	1 (2.0)	0 (0)	
Pelvic inflammatory desease	1 (0.4)	0 (0)	1 (0.5)	
Dermoid cyst	1 (0.4)	1 (2.0)	0 (0)	
Borderline malignant tumour	21 (8.8)	8 (16.3)	13 (6.8)	

Primary ovarian cancer	170 (71.1)	33 (67.3)	137 (72.1)
Malignant rare tumour	10 (4.2)	1 (2.0)	9 (4.7)
Metastatic ovarian cancer	9 (3.8)	1 (2.0)	8 (4.2)
Peritoneal carcinosis	1 (0.4)	0 (0)	1 (0.5)
No specific diagnosis suggested	8 (3.3)	1 (2.0)	7 (3.7)
Not possible	10 (4.2)	2 (4.1)	8 (4.2)

Results are presented as n (%) or median (range). *P-values denote the statistical significance of differences between cancers arising in endometriosis and not arising in endometriosis. [a] Solid component included the papillary projection, information available for 233/234 unilocular-solid, multilocular-solid and solid tumors. [b] Information available in 69/70 cases. [c] Information available in 235 cases. [d] Information available in 228 cases.