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Imaging in gynecological disease (14): clinical and ultrasound characteristics of ovarian clear cell carcinoma

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KEYWORDS: ovarian neoplasm; pure clear cell ovarian carcinoma; ultrasonography

ABSTRACT

Objective *To describe the clinical and ultrasound characteristics of ovarian pure clear cell carcinoma.*

Methods *This was a retrospective study involving data from 11 ultrasound centers. From the International Ovarian Tumor Analysis (IOTA) database, 105 patients who had undergone preoperative ultrasound examination by an experienced ultrasound examiner between 1999 and 2016 were identified with a histologically confirmed pure clear cell carcinoma of the ovary. An additional 47 patients diagnosed with pure clear cell carcinoma between 1999 and 2016 and with available complete preoperative ultrasound reports were identified retrospectively from the databases of the departments of gynecological oncology in the participating centers. The ultrasound images of all tumors were described using IOTA terminology. Clinical and ultrasound characteristics were analyzed for the whole group, and separately, for patients with and those without histologically confirmed endometriosis, and for patients with evidence of tumor developing from endometriosis.*

Results *Median age of the 152 patients was 53.5 (range, 28–92) years and 92/152 (60.5%) tumors were FIGO Stage I. Most tumors (128/152, 84.2%) were unilateral. On ultrasound examination, all tumors contained solid components and 36/152 (23.7%) were completely solid masses. The median largest diameter of the lesion was 117 (range, 25–310) mm. Papillary projections were present in 58/152 (38.2%) masses and, in most of these (51/56, 91.1%), vascularized papillary projections were seen. Information regarding the presence, site and type of pelvic endometriosis at histology was available for 130/152 patients. Endometriosis was noted in 54 (41.5%) of these. In 24/130 (18.6%) patients, the tumor was judged to have developed from endometriosis. Patients with, compared to those without, evidence of tumor developing from endometriosis were younger (median 47.5 vs 55.0 years, respectively), and ground-glass echogenicity of cyst fluid was more common in pure clear cell cancers developing from endometriosis (10/20 vs 13/79 (50.0% vs 16.5%), respectively).*

Conclusions *Ovarian pure clear cell carcinoma is usually diagnosed at an early stage and typically appears as a large unilateral mass with solid components. Patients with clear cell carcinoma developing from endometriosis are younger than other patients with clear cell carcinoma, and clear cell cancers developing from endometriosis more often manifest ground-glass echogenicity of cyst fluid.* *Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Aim

The aim of this study was to describe the clinical and ultrasound characteristics of pure clear cell carcinoma

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of the ovary. Tumors in which only clear cells are found on histological examination are defined as pure clear cell carcinomas, while admixtures of ovarian clear cell carcinoma with, for example, serous, mucinous, endometrioid or other tumor cells, are classified as clear cell carcinomas mixed with other histotypes[1].

Background

Epidemiology

Clear cell carcinoma of the ovary represents 5% to 25% of all epithelial ovarian cancers, depending on geographic location[2]. Substantial ethnic and/or racial differences in the distribution of different histological types of ovarian cancer are described in the literature. In Japan, ovarian clear cell carcinoma is more common than in western countries[3].

Patients with clear cell cancer are younger than those with high-grade serous cancers (median age 55 *vs* 64 years)[2,4]. A large proportion (25–58%) of clear cell carcinomas are diagnosed in women who have endometriosis[5–7]. About 30% of clear cell carcinomas show evidence of the tumor developing from endometriosis[8,9], and pathologists support the theory that endometriosis might be a precursor of clear cell carcinoma[10].

According to the dualistic model of epithelial ovarian carcinogenesis, clear cell carcinomas are Type-I tumors. Type-I tumors typically develop from benign tissue that implants in the ovary, for example, from endometrial implants in case of clear cell carcinoma. The implanted benign tissue may subsequently undergo malignant transformation in a slow, stepwise fashion. Type-II tumors (i.e. high-grade serous carcinomas) develop from intraepithelial carcinomas in the Fallopian tube, disseminating to the ovary and extra-ovarian sites with aggressive behavior[10].

Microscopy

Clear cell carcinomas display different microscopic patterns: papillary, tubulo-cystic and solid. Most tumors display a combination of all these patterns[9]. They are considered to have arisen from endometriosis if Sampson's criteria of malignant transformation are fulfilled[11]. Usually the focus of malignant transformation is found in a large protrusion of solid tissue in the cyst cavity[12]. All clear cell carcinomas are considered to be high-grade tumors[13].

Macroscopy

Clear cell carcinomas are usually large, up to 30 cm in diameter, with a mean size of 13–15 cm[12]. In most (92%) cases, they appear as unilateral masses[12]. They range from solid, to solid and cystic, to mainly cystic with fleshy, pale yellow nodules[13]. Clear cell carcinomas developing from endometriosis display the features of a cyst containing chocolate-colored fluid with a thickened polypoid or nodular area in the wall[12].

Clinical features and prognosis

Symptoms are usually explained by the presence of a pelvic or abdominal mass, and not by peritoneal spread[12]. A large unilateral ovarian mass is typically found, omentum and mesentery are seldom involved, and ascites and carcinomatosis are rare[10,13]. Reports show that 57–81% of clear cell carcinomas are diagnosed at FIGO Stage I or II[14,15]. Clear cell carcinomas have excellent prognosis when they are confined to the ovary. However, advanced stage clear cell carcinoma has a poorer prognosis than other epithelial ovarian cancers. This seems to be explained by clear cell carcinoma being less responsive to platinum-based chemotherapy[14,16]. Pectasides *et al.*[17] reported that the response rate to chemotherapy is lower for advanced stages of clear cell ovarian carcinoma than for advanced stages of serous carcinomas (45% *vs* 81%, respectively).

METHODS

This was a retrospective multicenter study including patients from 11 ultrasound centers (listed at the end of the main text). From the International Ovarian Tumor Analysis (IOTA) database, we identified patients with a histological diagnosis of ovarian pure clear cell carcinoma who had undergone preoperative ultrasound examination between 1999 and 2016[18–21]. Additional patients diagnosed with pure clear cell carcinoma between 1999 and 2016 and with available complete preoperative ultrasound reports were identified retrospectively from the databases of the departments of gynecological oncology in the participating centers. All patients had undergone preoperative ultrasound examination by an experienced ultrasound examiner who used the IOTA examination and measurement techniques and terminology[22] to describe the ultrasound images of the adnexal masses. 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.

In the case of bilateral adnexal masses, the mass with the most complex ultrasound morphology was used in the analysis. If both masses had similar ultrasound morphology, the largest mass or the one most easily accessible by ultrasound was included. According to the IOTA terminology, papillary projections were defined as solid tissue protruding into the cyst cavity from the cyst wall or from a septum with a height of 3 mm or more[22]. The largest solid component other than a papillary projection (i.e. solid tissue not protruding into the cyst cavity) was also measured. In some cases, a 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, in agreement with the IOTA consensus statement[22]. The presence of ascites and fluid in the pouch of Douglas was noted. 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)[22]. The specific diagnosis suggested by the ultrasound examiner in the original ultrasound report was recorded.

For women included in the IOTA studies, clinical and ultrasound information was obtained from the IOTA database, which contains data collected prospectively. For women who had been examined outside the IOTA studies, and in the case of missing information in the IOTA database, information was retrieved retrospectively from patient records and entered into an Excel file (Microsoft Office Excel 2007, Redmond, WA, USA) by the principal investigator at each center.

In addition to using the information collected in the IOTA database and patient records, one author with more than 10 years' experience in gynecological ultrasound (F.M.), assessed ultrasound images using pattern recognition[23], with the aim of identifying any typical ultrasound patterns of ovarian pure clear cell carcinoma. Only images of good quality were used for the pattern recognition assessment.

Final histology, FIGO stage[24], the presence of tumor developing from endometriosis (as judged by the local pathologist) and the presence of histologically confirmed endometriosis in the ipsilateral ovary or elsewhere in the pelvis were recorded. Clinical and ultrasound information was entered into a dedicated Excel file. Results are presented as absolute frequency (percentage) for nominal variables and as median (range) for continuous variables. The statistical difference in continuous data was determined using Mann–Whitney *U*-test or Kruskal–Wallis test and that in nominal data using χ^2 or Fisher's exact test, as appropriate. Statistical analyses were performed using the Statistical Package for Social Sciences software (PASW version 20.0, SPSS Statistic, IBM corp., New York, NY, USA). Two-sided tests were used and the significance level was set at $P < 0.05$.

RESULTS

We identified 105 patients with pure clear cell cancer of the ovary from the IOTA databases and another 47 patients examined outside the IOTA studies. There were no substantial differences in clinical or ultrasound characteristics between cases examined within and those examined outside the IOTA studies, except that fewer IOTA patients reported a history of oophorectomy, and more patients in the IOTA studies had ascites and free fluid in the pouch of Douglas (Tables S1 and S2). Therefore, results are presented for all 152 patients together.

Information regarding the presence, site and type of histologically confirmed pelvic endometriosis was available for 130 of the 152 patients. Endometriosis was found in 54/130 (41.5%) patients. In 24/130 (18.5%) of these, the pathologist judged the clear cell carcinoma to have developed from endometriosis, in 10/130 (7.7%) there was endometriosis in the ovary harboring the clear cell carcinoma but no signs of the cancer developing from endometriosis and in 20/130 (15.4%), endometriotic lesions were noted elsewhere in the pelvis.

Demographic data and tumor characteristics of all 152 cases are shown in Table 1. The median age at diagnosis was 53.5 (range, 28–92) years and 65/152 (42.8%) patients were premenopausal. Median serum CA 125 was 79.0 (range, 4.1–6410.0) U/mL. Most tumors were FIGO Stage I (92/152, 60.5%).

Demographic background data and tumor characteristics of the 130 cases with clear cell carcinoma for which information was available on endometriosis at histological examination are shown in Table 1. There were no substantial differences in clinical characteristics, except for age, between the four groups: patients without endometriosis, patients with evidence of tumor developing from endometriosis, patients with endometriosis in the same ovary but no evidence of tumor developing from endometriosis and patients with endometriosis elsewhere in the pelvis. Patients with cancer developing from endometriosis were younger than those with cancer not developing from endometriosis (median 47.5 *vs* 55.0 years, respectively).

Sonographic characteristics of the pure clear cell carcinomas in all 152 patients are described in Table 2. Most tumors (128/152, 84.2%) were unilateral, and their median largest diameter was 117 (range, 25–310) mm. Ascites was present in 32/152 (21.1%) patients. All clear cell carcinomas contained solid components, the median largest diameter of the largest solid component being 69 (range, 10–200) mm. Fifty-three (34.9%) of the 152 tumors were described as unilocular-solid, 63/152 (41.4%) as multilocular-solid and 36/152 (23.7%) as solid tumors (Figure 1). Papillary projections were present in 58/152 (38.2%) tumors. The majority of tumors with papillary projections contained more than three papillary projections (30/58, 51.7%), and most (51/56, 91.1%) were vascularized. The most common type of cyst fluid was of low-level echogenicity (50/115, 43.5%).

The original ultrasound examiner suggested a diagnosis of benign lesion in 7/152 (4.6%) cases, borderline ovarian tumor in 28/152 (18.4%) cases and malignant tumor in 117/152 (77.0%) cases. Two of the seven tumors misdiagnosed as benign were suspected to be endometriomas, two to be fibromas/fibrothecomas, one to be a teratoma, one an abscess and, in one case, a specific diagnosis was not suggested. Ultrasound images were available for two of the seven misclassified cancers (Figure S1).

Ultrasound characteristics of patients with and those without confirmation of pelvic endometriosis on histological examination are shown in Table 2 and Figure 2. There were no substantial differences in ultrasound characteristics between the four groups of patients, except for the type of echogenicity of cyst fluid. Clear cell cancers developing from endometriosis more often contained cyst fluid with ground-glass echogenicity than those not developing from endometriosis (10/20 (50.0%) *vs* 7/57

Table 1 Clinical and tumor characteristics in 152 cases of ovarian pure clear cell carcinoma and number of cases contributed by each participating center, overall and in 130 cases with histological information on endometriosis available, according to presence of endometriosis

			Evidence of endometriosis at histology (n = *54*)			
Characteristic	*All* (n = *152*)	*No evidence of endometriosis at histology* (n = *76*)	*Tumor developing from endometriosis* (n = *24*)	*Endometriosis in same ovary but tumor not developing from endometriosis* (n = *10*)	*Other pelvic endometriosis* (n = *20*)	P*
Age at diagnosis (years)	53.5 (28–92)	55 (32–92)	47.5 (32–72)	55 (37–80)	55 (35–77)	0.023
Premenopausal	65 (42.8)	28 (36.8)	16 (66.7)	4 (40.0)	9 (45.0)	0.084
Nulliparous†	61/123 (49.6)	29/57 (50.9)	10/20 (50.0)	4/8 (50.0)	9/19 (47.4)	0.995
Current hormonal therapy	10 (6.6)	2 (2.6)	3 (12.5)	0 (0)	4 (20.0)	0.025
Previous gynecological surgery						
Hysterectomy‡	3/115 (2.6)	0/63 (0)	0/11 (0)	0/4 (0)	1/15 (6.7)	0.154
Oophorectomy§	6/110 (5.5)	4/63 (6.3)	0/11 (0)	0/4 (0)	1/15 (6.7)	0.797
CA125 serum levels at diagnosis¶ (U/mL)	79.0 (4.1–6410.0)	168.5 (10–6410)	59 (4.1–1679)	31 (10–1635)	93.5 (12–1737)	0.223
FIGO stage						0.791
I	92 (60.5)	45 (59.2)	12 (50.0)	6 (60.0)	14 (70.0)	
II	18 (11.8)	8 (10.5)	4 (16.6)	1 (10.0)	4 (20.0)	
III	38 (25.1)	21 (27.6)	7 (29.2)	3 (30.0)	2 (10.0)	
IV	4 (2.6)	2 (2.6)	1 (4.2)	0 (0)	0 (0)	
Cases contributed per center						—
Tampa, FL, USA	1 (0.7)	0 (0)	0 (0)	0 (0)	1 (5.0)	
Barcelona, Spain	1 (0.7)	0 (0)	1 (4.2)	0 (0)	0 (0)	
Monza, Italy	6 (3.9)	1 (1.3)	0 (0)	4 (40.0)	1 (5.0)	
Prague, Czech Republic	7 (4.6)	0 (0)	0 (0)	0 (0)	0 (0)	
Milan (NCI), Italy	9 (5.9)	7 (9.2)	1 (4.2)	0 (0)	1 (5.0)	
Stockholm, Sweden	11 (7.2)	8 (10.5)	0 (0)	2 (20.0)	1 (5.0)	
Malmö, Sweden	12 (7.9)	6 (7.9)	2 (8.3)	1 (10.0)	3 (15.0)	
Leuven, Belgium	13 (8.6)	7 (9.2)	2 (8.3)	0 (0)	2 (10.0)	
Bologna, Italy	15 (9.9)	5 (6.6)	2 (8.3)	1 (10.0)	3 (15.0)	
Milan (EIO), Italy	31 (20.4)	14 (18.4)	14 (58.3)	2 (20.0)	1 (5.0)	
Rome, Italy	46 (30.2)	28 (36.8)	2 (8.3)	0 (0)	7 (35.0)	

Results are presented as median (range), *n* (%) or *n*/*N* (%). *Comparison, between four groups with histological information on endometriosis, by Kruskal–Wallis test for continuous variables and χ^2 or Fisher's exact test for nominal variables, as appropriate. Data were missing for some cases; numbers with data available in 'All' group and in group in which histological information on endometriosis was available, respectively, were: †123 and 104; ‡115 and 93; §110 and 93; and ¶127 and 109. EIO, European Institute of Oncology; FIGO, International Federation of Gynecology and Obstetrics[24]; NCI, National Cancer Institute.

(12.3%) in those without endometriosis, *vs* 3/8 (37.5%) in those with endometriosis in the same ovary but no evidence of tumor developing from endometriosis and *vs* 3/14 (21.4%) in those with endometriosis elsewhere in the pelvis).

Ultrasound images of high quality were available for 77/152 (50.7%) clear cell carcinomas. Using pattern recognition, no specific ultrasound pattern could be detected.

DISCUSSION

We have described the clinical and ultrasound characteristics of ovarian pure clear cell carcinomas. Median age at diagnosis was 53.5 years, 42.8% of the patients were premenopausal, and most tumors were FIGO Stage I. Most clear cell cancers were large unilateral tumors, all manifested solid components and almost 40% contained papillary projections. However, using pattern recognition, no ultrasound pattern specific to clear cell carcinoma could be detected. In 41.5% of patients, pelvic endometriosis was confirmed histologically and, in almost half of these, the pathologist judged the cancer to have developed from endometriosis. Patients with clear cell cancer developing from endometriosis were younger than those with clear cell cancer not developing from endometriosis. On ultrasound, clear cell carcinomas developing from endometriosis more often manifested ground-glass echogenicity of cyst fluid, but no other morphological differences were observed.

To the best of our knowledge, this is the largest study describing ultrasound features of ovarian pure clear cell carcinomas. One strength of this study is that it is multicenter and large, which increases the likelihood of our results being generalizable. Another strength is that all tumors were described in a standardized manner using IOTA terminology. A limitation of this study is that it is retrospective. Ultrasound images were not available for all

Table 2 Ultrasound characteristics and diagnosis suggested by original ultrasound examiner in 152 cases of ovarian pure clear cell carcinoma, overall and in 130 cases with histological information on endometriosis available, according to presence of endometriosis

Characteristic	*All* (n = *152*)	*No evidence of endometriosis at histology* (n = *76*)	*Evidence of endometriosis at histology* (n = *54*)			P*
			Tumor developing from endometriosis (n = *24*)	*Endometriosis in same ovary but tumor not developing from endometriosis* (n = *10*)	*Other pelvic endometriosis* (n = *20*)	
Unilateral	128 (84.2)	62 (81.6)	21 (87.5)	9 (90.0)	18 (90.0)	0.715
Ascites	32 (21.1)	18 (23.7)	3 (12.5)	2 (20.0)	5 (25.0)	0.677
Free fluid in pouch of Douglas	56 (36.8)	31 (40.8)	7 (29.2)	3 (30.0)	6 (30.0)	0.635
Largest diameter of lesion (mm)	117 (25–310)	117.5 (27–310)	125 (46–176)	113 (25–153)	129 (34–250)	0.455
Type of tumor						0.108
Unilocular-solid	53 (34.9)	20 (26.3)	13 (54.2)	6 (60.0)	8 (40.0)	
Multilocular-solid	63 (41.4)	37 (48.7)	7 (29.2)	2 (20.0)	6 (30.0)	
Solid	36 (23.7)	19 (25.0)	4 (16.7)	2 (20.0)	6 (30.0)	
Number of locules for multilocular-solid masses†						0.205
2	14/62 (22.6)	7/36 (19.4)	2/7 (28.6)	2/2 (100)	1/6 (16.7)	
3	8/62 (12.9)	6/36 (16.7)	1/7 (14.3)	0/2 (0)	0/6 (0)	
4–10	26/62 (41.9)	12/36 (33.3)	4/7 (57.1)	0/2 (0)	2/6 (33.3)	
> 10	14/62 (22.6)	11/36 (30.6)	0/7 (0)	0/2 (0)	3/6 (50.0)	
Echogenicity of cyst fluid in tumors not classified as solid‡						0.015
Anechoic	29/115 (25.2)	17/57 (29.8)	1/20 (5.0)	2/8 (25.0)	4/14 (28.6)	
Low level	50/115 (43.5)	24/57 (42.1)	9/20 (45.0)	3/8 (37.5)	7/14 (50.0)	
Ground glass	25/115 (21.7)	7/57 (12.3)	10/20 (50.0)	3/8 (37.5)	3/14 (21.4)	
Mixed	11/115 (9.6)	9/57 (15.8)	0/20 (0)	0/8 (0)	0/14 (0)	
Diameter of largest solid component (mm)§	69 (10–200)	74 (14–159)	61.5 (11–165)	65 (10–125)	75 (30–175)	0.399
Presence of papillary projection(s)	58 (38.2)	25 (32.9)	10 (41.7)	3 (30.0)	9 (45.0)	0.68
Number of papillary projections						0.499
1	15 (25.9)	5 (20.0)	4 (40.0)	1 (33.3)	2 (22.2)	
2	7 (12.1)	1 (4.0)	1 (10.0)	0 (0)	2 (22.2)	
3	6 (10.3)	2 (8.0)	0 (0)	1 (33.3)	1 (11.1)	
> 3	30 (51.7)	17 (68.0)	5 (50.0)	1 (33.3)	4 (44.4)	
Height of largest papillary projection (mm)	18 (3–65)	22 (4–61)	18 (5–57)	27 (6–65)	18 (5–35)	0.476
Papillation flow¶	51/56 (91.1)	24/24 (100)	9/9 (100)	3/3 (100)	7/9 (77.8)	0.039
Incomplete septum**	1/150 (0.7)	1/75 (1.3)	0/24 (0)	0/10 (0)	0/19 (0)	0.87
Shadowing	10 (6.6)	6 (7.9)	3 (12.5)	1 (10.0)	0 (0)	0.47
Color score**						0.279
1	8/150 (5.3)	4/75 (5.3)	0/23 (0)	0/10 (0)	2/20 (10.0)	
2	31/150 (20.7)	14/75 (18.7)	4/23 (17.4)	4/10 (40.0)	2/20 (10.0)	
3	67/150 (44.7)	31/75 (41.3)	10/23 (43.5)	4/10 (40.0)	13/20 (65.0)	
4	44/150 (29.3)	26/75 (34.7)	9/23 (39.1)	2/10 (20.0)	3/20 (15.0)	
Diagnosis on basis of subjective assessment by original ultrasound examiner						0.805
Benign	7 (4.6)	3 (3.9)	2 (8.3)	0 (0)	1 (5.0)	
Borderline	28 (18.4)	16 (21.1)	3 (12.5)	2 (20.0)	2 (10.0)	
Malignant	117 (77.0)	57 (75.0)	19 (79.2)	8 (80.0)	17 (85.0)	
Specific diagnosis suggested by original ultrasound examiner						0.814
Endometrioma	2 (1.3)	0 (0)	1 (4.2)	0 (0)	1 (5.0)	
Fibroma/fibrothecoma	2 (1.3)	2 (2.6)	0 (0)	0 (0)	0 (0)	
Other benign	2 (1.3)	1 (1.3)	1 (4.2)	0 (0)	0 (0)	
Borderline malignant tumor	25 (16.4)	12 (15.8)	4 (16.7)	1 (10.0)	3 (15.0)	
Primary ovarian cancer	92 (60.5)	44 (57.9)	15 (62.5)	7 (70.0)	14 (70.0)	
Metastatic ovarian cancer	4 (2.6)	4 (5.3)	0 (0)	0 (0)	0 (0)	
Other malignant	7 (4.6)††	4 (5.3)	0 (0)	0 (0)	1 (5.0)	
Not possible	11 (7.2)	5 (6.6)	3 (12.5)	2 (20.0)	1 (5.0)	
Not available	7 (4.6)	4 (5.3)	0 (0)	0 (0)	0 (0)	

Data presented as *n* (%), median (range) or *n*/*N* (%). *Comparisons, between four groups with histological information on endometriosis, by Kruskal–Wallis test for continuous variables and χ^2 or Fisher's exact test for nominal variables, as appropriate. †Data available for 62/63 cases in 'All' group and 51/52 cases with histological information on endometriosis available (*N*). ‡Data available for 115/116 cases in 'All' group. §Solid component includes papillary projections; data available for 151 cases overall. ¶Data available for 56/58 cases in 'All' group and 45/47 cases with histological information on endometriosis available. **Data available for 150 cases in 'All' group and 128 cases with histological information on endometriosis available. ††Six rare malignant tumors and one tubal carcinoma.

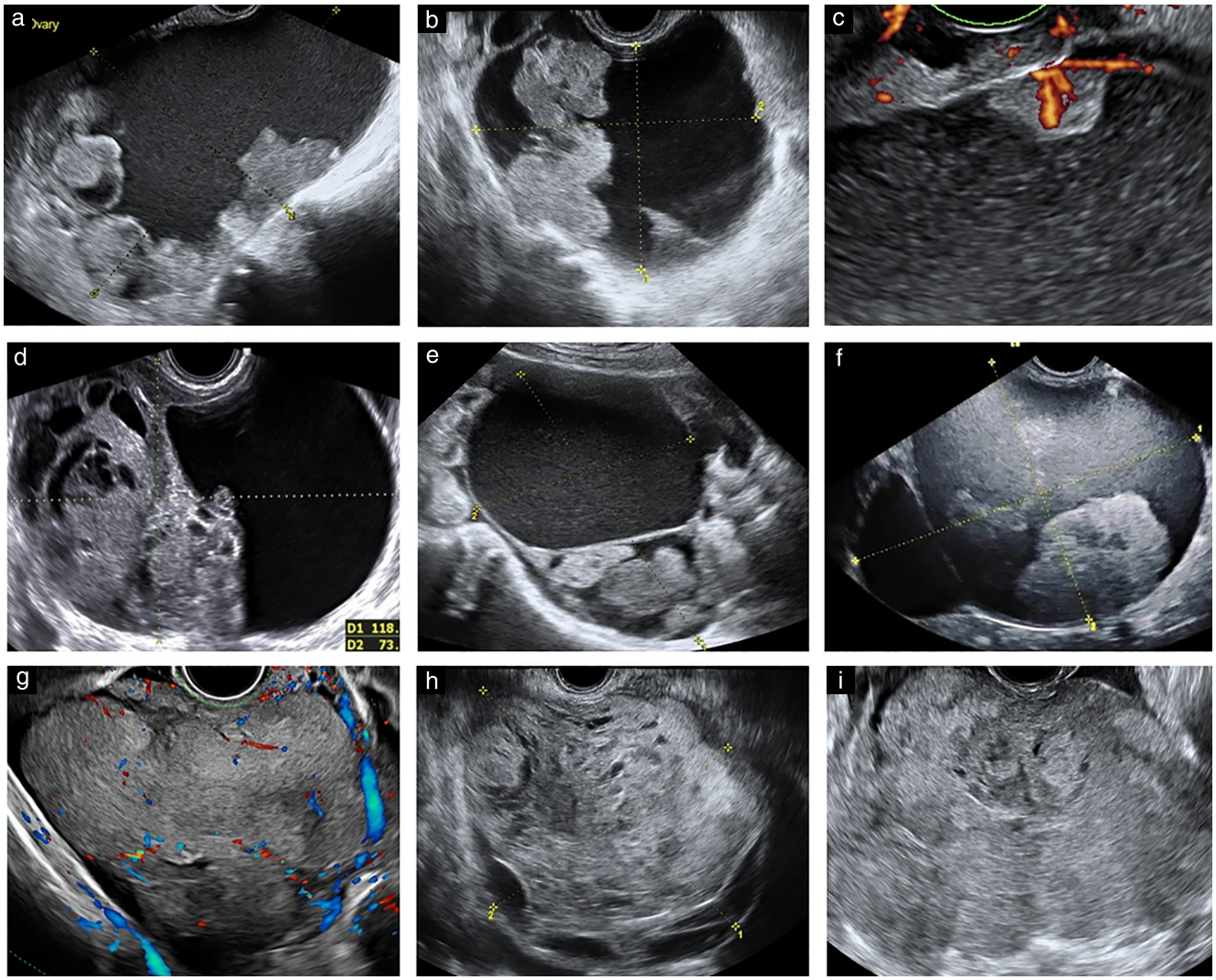

Figure 1 Ultrasound images showing ovarian pure clear cell carcinoma types described by original ultrasound examiner: unilocular-solid cyst (a–c), multilocular-solid cyst (d–f) and solid mass (g–i). Papillary projections were observed in some tumors (a,c,e,f).

cases, and this may have limited the possibility to detect ultrasound features specific to clear cell cancer.

The clinical findings of the current study agree with those of others[12,13] who noted that, compared with high-grade serous ovarian carcinomas, clear cell carcinomas present more often at an early stage, in patients who are younger and in premenopausal women. In agreement with Scarfone *et al.*[25], we found that patients with clear cell carcinoma showing evidence of the tumor developing from endometriosis were younger than other patients with clear cell carcinomas. Our ultrasound results agree well with the macroscopic appearance of clear cell carcinomas described in pathology textbooks: most were large, unilateral tumors described as solid, both solid and cystic or mainly cystic with solid nodules[13].

Our ultrasound findings agree with those of Alcazar *et al.*[26] who described the ultrasound features of 16 clear cell carcinomas and found that 15 were unilateral masses with solid components vascularized on color Doppler examination. Testa *et al.*[27] described the ultrasound findings in 15 malignancies developing from endometriomas. In their study, the proportion of tumors with papillary projections was higher than in the clear cell cancers developing from endometriomas in ours (86.7% *vs* 41.7%). This might be explained by Testa *et al.*[27] including not only clear cell carcinomas ($n = 6$), but also endometrioid cancers ($n = 5$) and borderline tumors ($n = 4$) developing from endometriosis.

Clear cell carcinomas have some clinical and pathological features similar to those of endometrioid carcinomas[28]. Both are diagnosed more often in premenopausal patients than are the much more common serous carcinomas[12,29] and both are frequently found at an early stage (FIGO Stage I). Both histotypes are considered Type-I tumors with indolent behavior, and endometriosis has been described as a possible precursor for both[10]. Endometrioid ovarian cancers and ovarian pure clear cell cancers also have similar ultrasound characteristics. Most are large unilateral tumors with solid components, and papillary projections are common[28]. Papillary projections are particularly common in endometrioid (46.9%)[28] and clear cell

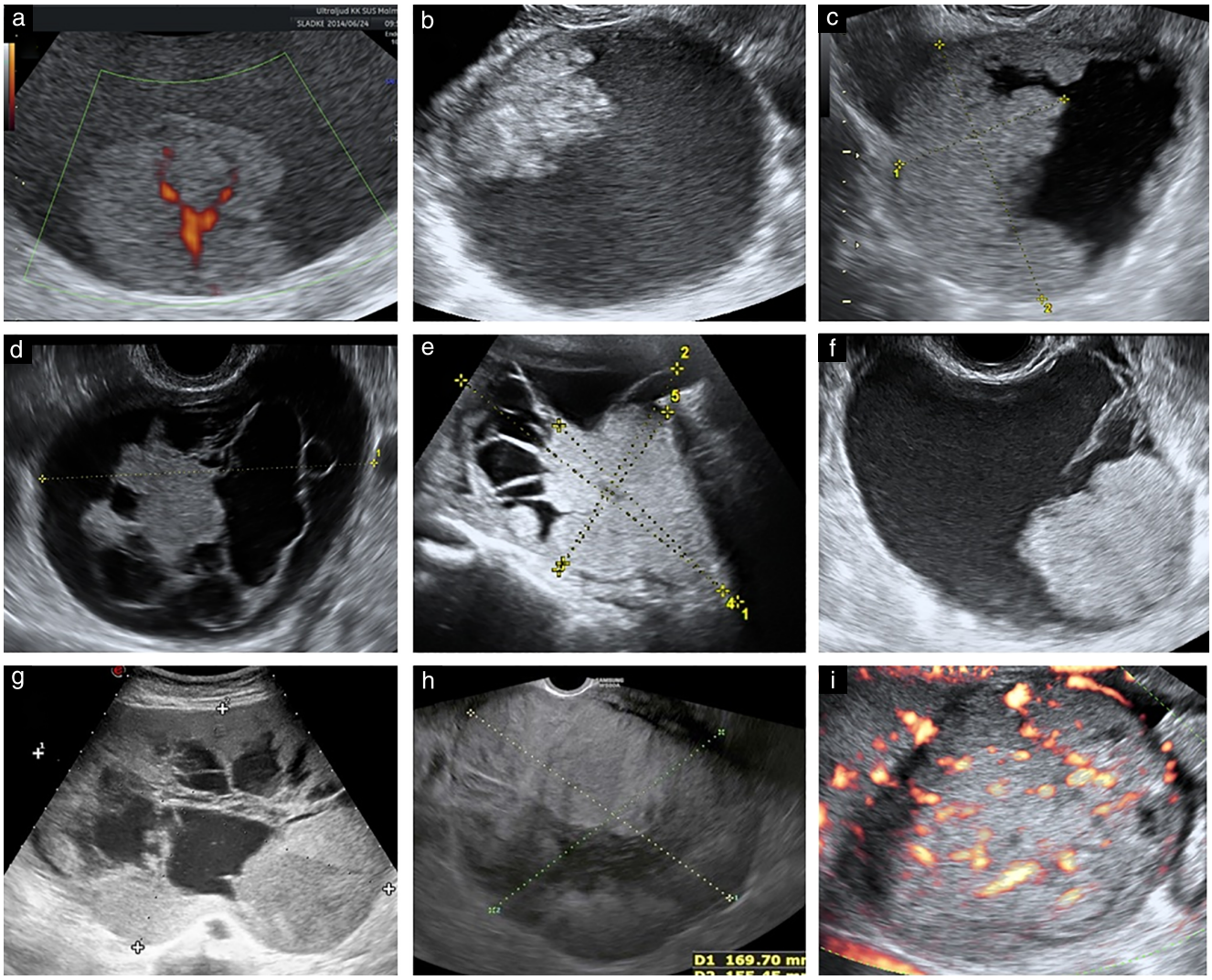

Figure 2 Ultrasound images of ovarian pure clear cell carcinomas in patients with histologically confirmed pelvic endometriosis, described as unilocular-solid cyst (a–c), multilocular-solid cyst (d–f) or solid mass (g–i). Images in (a) and (f) show tumors developing from endometriosis, while (c) shows tumor with endometriotic foci in ovary harboring clear cell carcinoma but no signs of cancer developing from endometriosis. Tumors in (b,d,e,g–i) were associated with histologically confirmed endometriosis outside the ovary harboring clear cell cancer.

(41.7%) carcinomas developing from endometriosis. Papillary projections are typical ultrasound features of serous and mucinous endocervical-type borderline tumors[30], and this could explain why many clear cell carcinomas (18%) and endometrioid ovarian cancers (11%)[28] were misdiagnosed as borderline tumors by the original ultrasound examiner. In our study on endometrioid ovarian cancers, we found that many endometrioid cancers not developing from endometriosis had a cockade-like appearance on ultrasound, i.e. a large central solid component entrapped within locules[28]. For clear cell carcinomas, we could not identify any specific ultrasound pattern. Because endometrioid and clear cell cancers of the ovary present similarly clinically and look similar on ultrasound, we do not believe that it would be possible to discriminate between these two cancer types preoperatively. However, it should be possible to distinguish endometrioid or clear cell cancer of the ovary from serous ovarian cancer (especially high-grade serous cancer) and mucinous ovarian cystadenocarcinoma because of differences in clinical presentation and ultrasound features[28,29,31]. It should at least be possible to evaluate which diagnosis is the most likely. High-grade serous carcinomas are more often bilateral than clear cell carcinomas; they are multilocular-solid or solid lesions that very rarely contain papillary projections[29]. Mucinous ovarian carcinomas are much larger than serous, endometrioid and clear cell carcinomas, virtually always unilateral and contain a very large number of cyst locules, but papillary projections are very rare[31]. Preoperative discrimination between different types of ovarian malignancy can be of clinical importance. For example, knowing the most likely type of malignancy may affect patient counseling (prognosis, most likely type of surgery, possibility of conservative surgery in young patients with Stage-I clear cell carcinoma[32], which tumor markers to test). Clear cell carcinoma is less sensitive to platinum-based chemotherapy[14,16] than serous and endometrioid adenocarcinomas and, if it were possible to identify clear cell tumors preoperatively, this

could assist the oncology surgeon in making maximal efforts to obtain zero residual disease. The typical ultrasound appearance of different ovarian malignancies has been described in the Imaging in Gynecological Disease series of this journal (see Virtual Issue https://obgyn.onlinelibrary.wiley.com/doi/toc/10.1002/(ISSN)1469-0705.IMAGINGINGYNECOLOGICALDISEASE)[28,29,31,33–38]. It remains to be shown in prospective studies if different types of ovarian malignancy, including epithelial ovarian cancer, i.e. serous, mucinous, endometrioid, clear cell and undifferentiated cancers, can be distinguished on the basis of clinical information and ultrasound appearance. However, before starting any prospective study, the typical ultrasound appearance of different types of ovarian malignancy should be identified.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Clinical and tumor characteristics in 152 cases of pure ovarian clear cell carcinoma, overall and according to whether they were included in International Ovarian Tumor Analysis (IOTA) studies

Table S2 Ultrasound characteristics and diagnosis suggested by the original ultrasound examiner in 152 cases of pure ovarian clear cell carcinoma, overall and according to whether they were included in International Ovarian Tumor Analysis (IOTA) studies

Figure S1 Ultrasound images of two pure clear cell carcinomas suggested to be benign lesions by original ultrasound examiner. Abscess was suspected in (a) and endometrioma in (b).