Clinical and ultrasound characteristics of surgically removed adnexal lesions with largest diameter ≤ 2.5 cm: a pictorial essay

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ABSTRACT

Objectives To describe the ultrasound characteristics, indications for surgery and histological diagnoses of surgically removed adnexal masses with a largest diameter of ≤ 2.5 cm (very small tumors), to estimate the sensitivity and specificity of diagnosis of malignancy by subjective assessment of ultrasound images of very small tumors and to present a collection of ultrasound images of surgically removed very small tumors, with emphasis on those causing diagnostic difficulty.

Methods Information on surgically removed adnexal tumors with a largest diameter of ≤ 2.5 cm was retrieved from the ultrasound databases of seven participating centers. The ultrasound images were described using the International Ovarian Tumor Analysis terminology. The original diagnosis, based on subjective assessment of the ultrasound images by the ultrasound examiner, was used to calculate the sensitivity and specificity of diagnosis of malignancy.

Results Of the 129 identified adnexal masses with largest diameter ≤ 2.5 cm, 104 (81%) were benign, 15 (12%) borderline malignant and 10 (8%) invasive tumors. The main indication for performing surgery was suspicion of malignancy in 22% (23/104) of the benign tumors and in all 25 malignant tumors. None of the malignant tumors was a unilocular cyst (vs 50% of the benign tumors), all malignancies contained solid components (vs 43% of the benign tumors), 80% of the borderline tumors had papillary projections (vs 21% of the benign tumors and 20% of the invasive malignancies) and all invasive tumors and 80% of the borderline tumors were vascularized on color/power Doppler examination (vs 44% of the benign tumors). The ovarian crescent sign was present in 85% of the benign tumors, 80% of the borderline tumors and 50% of the invasive malignancies. The sensitivity of diagnosis of malignancy by subjective assessment of ultrasound images was 100% (25/25) and the specificity was 86% (89/104). Excluding unilocular cysts, the specificity was 71% (37/52). Analysis of images illustrated the difficulty in distinguishing benign from borderline very small cysts with papillations and benign from malignant very small well vascularized (color score 3 or 4) solid adnexal tumors.

Conclusions Very small malignant tumors manifest generally accepted ultrasound signs of malignancy. Small unilocular cysts are usually benign, while small non-unilocular masses, particularly ones with solid components, incur a risk of malignancy and pose a clinical dilemma.

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INTRODUCTION

Transvaginal ultrasound is considered the first-line imaging method for the diagnosis of adnexal masses. Subjective assessment of ultrasound images, mathematical models (such as the logistic regression models developed by the International Ovarian Tumor Analysis (IOTA) group), ultrasound rules (such as the Simple Rules of the...
IOTA group) or scoring systems (such as the Risk of Malignancy Index), can be used to discriminate between benign and malignant adnexal masses\(^1\–7\). The ability of these methods to discriminate between benign and malignant adnexal masses has been reported to be poorer in small (maximum diameter \(< 4\) cm) and large (maximum diameter \(\geq 10\) cm) adnexal masses than in masses of moderate size (4.0–9.9 cm), with sensitivity being poorest for small tumors\(^8\). Surgical management of very small lesions is a challenge, particularly in young women with childbearing potential. The surgical strategy may be conservative cystectomy (worsening the prognosis owing to risk of spillage if the tumor is malignant, and causing harm by damaging the ovarian reserve if the tumor is benign) or adnexectomy (with the risk of overtreatment in patients with a benign tumor)\(^9\).

In this study, we define as ‘very small’ a tumor with a largest diameter of 2.5 cm or less. If we had chosen to study tumors of \(\leq 1\) cm, \(\leq 1.5\) cm or \(\leq 2\) cm, the number of tumors would have been too small to enable a meaningful analysis. Moreover, tumors of \(\leq 2.5\) cm are small enough to be contained within the ovarian stroma of a premenopausal ovary, so that one would expect to see normal ovarian stroma surrounding the lesion, at least in women of fertile age.

The aim of this study was to describe the ultrasound characteristics, indications for surgery and histological diagnoses of surgically removed ‘very small’ adnexal masses, i.e. those with a largest diameter of \(\leq 2.5\) cm, to estimate the sensitivity and specificity of subjective assessment of ultrasound images of very small tumors with regard to malignancy, and to present a collection of ultrasound images of surgically removed very small tumors, with particular emphasis on those difficult to classify as benign or malignant by the examiner.

**METHODS**

One hundred and twenty-nine patients with an adnexal tumor of \(\leq 2.5\) cm on transvaginal ultrasound, that was surgically removed within 120 days of the ultrasound examination and with a histological diagnosis available, were identified from the databases of seven participating centers (Table S1). All ultrasound examinations were carried out between 1999 and 2014. Of the 129 patients, 87 (67%) had been examined within the frame of the IOTA study using a standardized examination technique and following a strict research protocol that included a meaningful analysis. Moreover, tumors of \(\leq 2.5\) cm are small enough to be contained within the ovarian stroma of a premenopausal ovary, so that one would expect to see normal ovarian stroma surrounding the lesion, at least in women of fertile age.

The remaining 42 (33%) patients had undergone a clinical ultrasound examination outside the IOTA studies, however the ultrasound examination technique and the terminology used to describe the ultrasound findings in the reports of these patients were similar to those used in the IOTA studies. All ultrasound examinations were carried out by gynecologists with Level-2 or Level-3 ultrasound experience\(^{13}\) using high-end ultrasound equipment, i.e. Esaote Technos My Lab 70 X Vision (Esaote S.p.a, Genova, Italy) with a 3–9-MHz transvaginal transducer, Medison Accuvix V20 Prestige (Samsung Medison Co, Ltd, Seoul, Korea) with a 4–9-MHz transvaginal transducer, GE Voluson E8 (GE Medical Systems, Zipf, Austria) with a 5–9-MHz transvaginal transducer or Acuson Sequoia 512 (Siemens Medical Solutions, Mountain View, CA, USA) with a 4–8-MHz transvaginal transducer. The color/power Doppler settings were specific for each ultrasound system but were kept the same on each system in all examinations. The pulse repetition frequency used varied from 0.3 to 0.9 kHz. The color gain was set just below the level at which background noise appears. For the 42 patients not included in the IOTA studies, an ultrasound examiner (P.P., M.E.C., R.M. or M.L.), from the center in which the examination took place, reviewed the original ultrasound reports and all digital or printed ultrasound images and videoclips and described the adnexal masses using the IOTA terms and definitions\(^{14}\). In some cases the reviewer had also performed the ultrasound examination. Information on the level of diagnostic confidence and the diagnosis suggested by the original ultrasound examiner was retrieved from the original ultrasound reports. In case of bilateral masses, the mass with the most complex ultrasound morphology was included in our analysis.

Clinical information not available in the IOTA database or in the ultrasound reports was retrieved from patient records, including previous gynecological surgery, symptoms, levels of serum CA 125 (in U/mL), indication for surgery, surgical approach and histological diagnosis of the mass. The decision to operate was made by the referring physician taking all clinical and ultrasound information into account, and the indications for surgery were obtained from the patient records. If more than one indication was stated in the record, one main indication was chosen using the following priority order: suspicion or uncertainty about malignancy, symptoms (including infertility), increased CA 125 levels and personal or family history of ovarian or breast cancer or being a BRCA mutation carrier.

A woman was considered to be postmenopausal if she reported a spell of at least 12 months of amenorrhea after the age of 40 years, provided that medication or disease did not explain the amenorrhea. Women 50 years or older who had undergone hysterectomy were...
also defined as postmenopausal. Women who had had a menstrual period during the year before the examination and women who were younger than 50 years of age and had undergone a hysterectomy without bilateral oophorectomy were defined as premenopausal.

The stage of malignant tumors was described using the criteria of the International Federation of Gynecology and Obstetrics. When calculating sensitivity and specificity, borderline tumors were classified as malignant. Owing to the retrospective nature of the study, ethical committee approval was not deemed to be necessary.

RESULTS

Patient characteristics are shown in Table 1. Median age was 42 years, 49% (61/124) of the patients were nulliparous and 33% (43/129) were postmenopausal. Symptoms were present in 60/129 (47%) women, the most common symptoms being pain (39/129 (30%)) and abnormal vaginal bleeding (11/129 (9%)).

The ultrasound features of the very small adnexal lesions are shown in Table 2. Half of the benign lesions were unilocular cysts while none of the borderline or invasive tumors was unilocular. Ninety percent (9/10) of the invasive tumors were solid tumors vs 20% (3/15) of the borderline tumors and 19% (20/104) of the benign tumors. Most (11/15 (73%)) borderline tumors were unilocular solid lesions vs 21/104 (20%) of the benign lesions and 1/10 (10%) of the invasive tumors. Papillary projections were present in 12/15 (80%) of the borderline tumors, 22/104 (21%) of the benign lesions and 2/10 (20%) of the invasive tumors. ‘Ground-glass’ echogenicity was as common in borderline tumors (4/15 (27%)) as in benign tumors (31/104 (30%)). All invasive tumors and 80% (12/15) of the borderline tumors were vascularized on color/power Doppler examination, vs 44% (46/104) of the benign lesions (14/52 (27%) unilocular and 32/52 (62%) non-unilocular). In masses with available information on the ovarian crescent sign (n = 117), this was observed in 85% (78/92) of benign lesions, 80% (12/15) of borderline tumors and 50% (5/10) of invasive tumors.

Indications for surgery, as noted in patient records, are described in Table 3. In almost half (45/104 (43%)) of the patients with benign lesions, the main indication for surgery was symptoms (including infertility), in 23/104 (22%) it was suspicion of or uncertainty about malignancy and in the remaining patients the indications varied, e.g. raised CA 125 levels, personal or family history of ovarian cancer or being a BRCA mutation carrier. The indication for surgery was unclear in 20% (21/104) of the patients with benign masses. In all 25 patients with a borderline or malignant tumor, the main indication for surgery was suspicion of malignancy (in one of these cases the primary indication for surgery was endometrial cancer with suspicion of metastasis to the ovary, but the histological diagnosis of the ovarian mass was synchronous ovarian endometrioid cancer).

Most patients (110/129 (85%)) underwent laparoscopic surgery, 15 (12%) underwent laparotomy, while in four (3%) patients the surgical approach was not

Table 1 Clinical characteristics of 129 patients undergoing surgery for very small adnexal lesions

| Variable                              | All (n = 129) | Unilocular cyst (n = 52) | Non-unilocular cyst (n = 77) |
|---------------------------------------|--------------|--------------------------|-------------------------------|
| Age (years)                           | 42 (8–80)    | 35.5 (18–73)             | 51 (8–80)                     |
| Postmenopausal                        | 43 (33.3)    | 5 (9.6)                  | 38 (49.3)                    |
| Nulliparous*                          | 61/124 (49.2)| 28/51 (54.9)            | 33/73 (45.2)                  |
| Personal history of ovarian cancer    | 13 (10.1)    | 1 (1.9)                  | 12 (15.6)                     |
| Personal history of breast cancer‡    | 9/128 (7.0)  | 2/51 (3.9)              | 7/77 (9.1)                    |
| Previous hysterectomy                 | 4 (3.1)      | 1 (1.9)                  | 3 (3.9)                       |
| Previous unilateral salpingo-oophorectomy* | 17/121 (14.0)| 5/47 (10.6)            | 12/74 (16.2)                  |
| Current hormonal therapy              | 20 (15.5)    | 14 (26.9)                | 6 (7.8)                       |
| CA 125 serum level (U/mL)†            | 16 (0–1808)  | 10 (5–200)               | 16 (0–1808)                   |
| Presenting symptoms:                  | 60 (46.5)    | 32 (61.5)                | 28 (36.4)                     |
| Pain                                  | 39 (30.2)    | 28 (53.8)                | 11 (14.3)                     |
| Abnormal vaginal bleeding             | 11 (8.5)     | 3 (5.8)‡                 | 8 (10.4)§                     |
| Virilization                          | 3 (2.3)      | 0 (0.0)                  | 3 (3.9)                       |
| Infertility                           | 1 (0.8)      | 1 (1.9)                  | 0 (0.0)                       |
| Abdominal pressure                    | 2 (1.6)      | 0 (0.0)                  | 2 (2.6)                       |
| Abdominal bloating                    | 1 (0.8)      | 0 (0.0)                  | 1 (1.3)                       |
| Fever                                 | 1 (0.8)      | 0 (0.0)                  | 1 (1.3)                       |
| Amenorrhea                            | 1 (0.8)      | 0 (0.0)                  | 1 (1.3)                       |
| Swollen legs                          | 1 (0.8)      | 0 (0.0)                  | 1 (1.3)                       |
| Absence of symptoms                   | 63 (48.8)    | 16 (30.8)                | 47 (61.0)                      |
| Information on symptoms lacking/not specified | 6 (4.7) | 4 (7.7) | 2 (2.6) |

Data are given as n (%), n/N (%) or median (range). *Data missing. †Data available for 74 patients (19 with unilocular and 55 with non-unilocular cyst). §Cystadenoma (n = 2, one in a patient operated on for endometrial carcinoma), salpingitis (n = 1). ¶Cystadenomalocystadenofibroma (n = 2), fibrothecoma (n = 2), primary ovarian cancer synchronous to endometrial cancer (n = 1), granulosa cell tumor (n = 1), ovarian stromal hyperplasia with stromal hyperthecosis (n = 1), paraovarian cyst (n = 1, detected during operation for endometrial carcinoma).
Table 2: Sonographic characteristics of tumors in 129 women with benign, borderline (BOT) or malignant very small adnexal lesions

| Variable                        | All (n = 129) | Unilocular (n = 52) | Non-unilocular (n = 52) | BOT (n = 15) | Malignant (n = 10) |
|---------------------------------|--------------|--------------------|------------------------|-------------|-------------------|
| Largest diameter (mm)           | 21 (6–25)*   | 20.5 (6–25)        | 22 (9–25)              | 20 (8–25)   | 21.5 (15–25)      |
| Type of tumor                   |              |                    |                        |             |                   |
| Unilocular                      | 52 (40.3)    | 52 (100.0)         | 0 (0.0)                | 0 (0.0)     | 0 (0.0)           |
| Unilocular solid                | 33 (26.5)    | 21 (40.4)          | 0 (0.0)                | 11 (73.3)   | 1 (10.0)          |
| Multilocular                    | 7 (5.4)      | 0 (0.0)            | 7 (13.5)               | 0 (0.0)     | 0 (0.0)           |
| Multilocular solid              | 5 (3.9)      | 0 (0.0)            | 4 (7.7)                | 1 (6.7)     | 0 (0.0)           |
| Solid                           | 32 (24.8)    | 0 (0.0)            | 20 (38.5)†             | 3 (20.0)    | 9 (90.0)          |
| Cyst content                    |              |                    |                        |             |                   |
| Anechoic                         | 34 (26.4)    | 6 (11.5)           | 21 (40.4)              | 6 (40.0)    | 1 (10.0)          |
| Low level                        | 16 (12.4)    | 9 (17.3)           | 4 (7.7)                | 2 (13.3)    | 1 (10.0)          |
| Ground glass                     | 35 (27.1)    | 26 (50.0)          | 5 (9.6)                | 4 (26.7)    | 0 (0.0)           |
| Hemorrhagic                      | 3 (2.3)      | 3 (5.8)            | 0 (0.0)                | 0 (0.0)     | 0 (0.0)           |
| Mixed                            | 10 (7.8)     | 8 (15.4)           | 2 (3.8)                | 0 (0.0)     | 0 (0.0)           |
| No cyst fluid                    | 31 (24.0)    | 0 (0.0)            | 20 (38.5)              | 3 (20.0)    | 8 (80.0)          |
| Bilateral mass                   | 21 (16.3)    | 8 (15.4)           | 7 (13.5)               | 3 (20.0)    | 3 (30.0)          |
| Presence of papillary projections‡| 36 (27.9)    | 0 (0.0)            | 22 (42.3)              | 12 (80.0)   | 2 (20.0)          |
| Number of papillations           |              |                    |                        |             |                   |
| 1                               | 26 (20.2)    | —                  | 16 (30.8)              | 8 (53.3)    | 2 (20.0)          |
| 2                               | 5 (3.9)      | —                  | 4 (7.7)                | 1 (6.7)     | 0 (0.0)           |
| 3                               | 5 (3.9)      | —                  | 2 (3.8)                | 3 (20.0)    | 0 (0.0)           |
| Papillation contour              |              |                    |                        |             |                   |
| Smooth                           | 13 (10.1)    | —                  | 8 (15.4)               | 4 (26.7)    | 1 (10.0)          |
| Irregular                        | 23 (18.7)    | —                  | 14 (26.9)              | 8 (53.3)    | 1 (10.0)          |
| Height of largest papillation (mm)| 7 (3–17)    | —                  | 6 (3–15)               | 9 (4–17)    | 3.5 (3–4)         |
| Vascularization in papillation   | 19 (14.7)    | —                  | 8 (15.4)               | 9 (60.0)    | 2 (20.0)          |
| Solid component                  | 70 (54.3)    | 0 (0.0)            | 45 (86.5)              | 15 (100.0)  | 10 (100.0)        |
| Maximum diameter of largest solid component (mm)| 14.5 (3–25) | — | 15 (4–25) | 12 (4–22) | 20 (3–25) |
| Number of locules                |              |                    |                        |             |                   |
| 0                               | 31 (24.0)    | 52 (100.0)         | 20 (38.5)              | 3 (20.0)    | 8 (80.0)          |
| 1                               | 83 (65.9)    | 0 (0.0)            | 21 (40.4)              | 11 (73.3)   | 2 (20.0)          |
| 2                               | 6 (4.7)      | 0 (0.0)            | 4 (7.7)                | 1 (6.7)     | 0 (0.0)           |
| ≥ 3                             | 7 (5.4)      | 0 (0.0)            | 7 (13.5)               | 0 (0.0)     | 0 (0.0)           |
| Incomplete septum               | 5 (3.9)      | 2 (3.8)            | 3 (5.8)                | 0 (0.0)     | 0 (0.0)           |
| Color score                     |              |                    |                        |             |                   |
| No vascularization               | 61 (47.3)    | 38 (73.1)          | 20 (38.5)              | 3 (20.0)    | 0 (0.0)           |
| Minimal vascularization         | 38 (29.5)    | 10 (19.2)          | 16 (30.8)              | 6 (40.0)    | 6 (60.0)          |
| Moderate vascularization        | 20 (15.5)    | 4 (7.7)            | 10 (19.2)              | 5 (33.3)    | 1 (10.0)          |
| Abundant vascularization        | 10 (7.8)     | 0 (0.0)            | 6 (11.5)               | 1 (6.7)     | 3 (30.0)          |
| Shadowing                       | 20 (15.5)    | 5 (9.6)            | 13 (25.0)              | 1 (6.7)     | 1 (10.0)          |
| Ovarian crescent sign§          | 95/117 (81.2)| 41/43 (95.3)       | 37/49 (75.5)           | 12 (80.0)   | 5 (50.0)          |
| Mobility§                       |              |                    |                        |             |                   |
| Mobile                          | 43/63 (68.3)| 18/30 (60.0)       | 16/19 (84.2)           | 6/9 (66.7)  | 3/5 (60.0)        |
| Reduced mobility                | 13/63 (20.6)| 7/30 (23.3)        | 3/19 (15.8)            | 3/9 (33.3)  | 0/5 (0.0)         |
| Fixed                           | 7/63 (11.1) | 5/30 (16.7)        | 0/19 (0.0)             | 0/9 (0.0)   | 2/5 (40.0)        |
| Tender mass at US§              | 66/127 (52.0)| 29/50 (58.0)       | 27/51 (53.9)           | 6/40 (15.0) | 4/40 (10.0)       |
| Fluid in pouch of Douglas       | 24 (18.6)    | 7 (13.5)           | 5 (9.6)                | 5 (33.3)    | 7 (70.0)          |
| Ascites                         | 1 (0.8)      | 0 (0.0)            | 0 (0.0)                | 0 (0.0)     | 1 (10.0)          |

Data are given as n (%), n/N (%) or median (range). *Three lesions ≤ 1 cm, 14 lesions 1.1–1.5 cm, 30 lesions 1.6–2.0 cm and 82 lesions 2.1–2.5 cm. †Fibroma/fibrothecoma (n = 7), teratoma (n = 3), Leydig cell tumor (n = 3), functional cyst (n = 1), cystadenoma (n = 1), struma ovarii (n = 1), steroid cell tumor (n = 1), stromal hyperplasia with stromal hyperthecosis (n = 1), calcified benign tissue (n = 1), normal ovarian parenchyma (n = 1). ‡Papillations described in unilocular solid malignant lesion and in cyst locule in one of the solid lesions (solid tumors may contain cystic spaces, the definition of solid tumor being that it consists of at least 80% solid tissue14). §Data missing. US, ultrasound scan.

The surgical procedures were adnexectomy (n = 61 (47%)), cystectomy (n = 47 (36%)), radical oncological surgery for malignancy (n = 7 (5%)), salpingectomy (n = 5 (4%)), hysterectomy and bilateral adnexectomy (n = 3 (2%)), oophorectomy (n = 2 (1.6%)), ovarian biopsy (n = 1 (1%)) and diagnostic laparoscopy (revealing only adhesions, in which case the diagnosis was peritoneal inclusion cyst, n = 1 (1%)). In two cases (1.6%), the surgical procedure was not recorded.

The histological diagnoses of the very small adnexal lesions are shown in Table 4. Most lesions (104/129 (81%)) were benign. The most common benign diagnoses...
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Table 3 Indication for surgery in 129 women with benign, borderline (BOT) or malignant very small adnexal lesions

| Parameter | All (n = 129) | Benign (n = 104) | Unilocular (n = 52) | Non-unilocular (n = 52) | BOT (n = 15) | Malignant (n = 10) |
|-----------|--------------|-----------------|---------------------|------------------------|-------------|-----------------|
| Suspicion of adnexal malignancy | 38 (29.5) | 0 (0.0) | 13 (25.0) | 15 (100.0) | 10 (100.0) | |
| Uncertainty about adnexal malignancy | 10 (7.8) | 1 (1.9)* | 9 (17.3) | 0 (0.0) | 0 (0.0) | |
| Symptoms (including infertility) | 45 (34.9) | 34 (65.4) | 11 (21.2) | 0 (0.0) | 0 (0.0) | |
| Increased CA 125 levels | 7 (5.4) | 4 (7.7)† | 3 (5.8)‡ | 0 (0.0) | 0 (0.0) | |
| Personal or family history of ovarian/breast cancer, or BRCA mutation carrier | 5 (3.9) | 3 (5.8) | 2 (3.8) | 0 (0.0) | 0 (0.0) | |
| Endometrial cancer | 2 (1.6) | 1 (1.9) | 1 (1.9) | 0 (0.0) | 0 (0.0) | |
| Opportunistic removal of cyst | 1 (0.8) | 1 (1.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Unclear | 21 (16.3) | 8 (15.4) | 13 (25.0) | 0 (0.0) | 0 (0.0) | |

Data are given as n (%). *Cyst detected in premenopausal patient referred for restaging surgery after histological diagnosis of ovarian carcinoma in endometriotic cyst. Examiner was uncertain about malignancy because cyst was found in ovary from which ovarian carcinoma had been removed and cyst contents were ground glass. †Endometrioma (n = 2), functional cyst (n = 1), peritoneal cyst (n = 1, CA 125 levels: 64–200 U/mL). ‡Endometrioma (n = 1), functional cyst (n = 1), cystadenofibroma (n = 1, CA 125 levels: 38–1808 U/mL).

Table 4 Histological findings of surgically removed very small adnexal lesions in 129 women

| Histology | All (n = 129) | Unilocular cyst (n = 52) | Non-unilocular lesion (n = 77) |
|-----------|--------------|------------------------|-------------------------------|
| Benign tumor and tumor-like lesion | 104 (80.6) | 52 (100.0) | 52 (67.5) |
| Endometrioma | 26 | 21 | 5 |
| Teratoma | 14 | 8 | 6 |
| Cystadenofibroma | 12 | 2 | 10 |
| Serous cystadenoma | 11 | 2 | 9 |
| Functional cyst | 8 | 5 | 3 |
| Fibroma/fibrotheca | 7 | 0 | 7 |
| Hydrosalpinx/salpingitis | 6 | 5 | 1 |
| Simple cyst/inclusion cyst | 6 | 4 | 2 |
| Leydig cell tumor | 3 | 0 | 3 |
| Paraovarian/salpingeal cyst | 2 | 1 | 1 |
| Peritoneal cyst | 2 | 2 | 0 |
| Mucinous cystadenoma | 1 | 1 | 0 |
| Struma ovarii | 1 | 0 | 1 |
| Steroid cell tumor | 18 | 10 | 1 |
| Struma ovarii | 1 | 0 | 1 |
| Normal ovarian parenchyma | 1 | 0 | 1 |
| Borderline tumor | 15 (11.6) | 0 (0.0) | 15 (19.5) |
| Primary Stage I | 7 | — | 7 |
| Recurrent Stage I | 5 | — | 5 |
| Recurrent Stage II | 2 | — | 2 |
| Recurrent Stage III | 1 | — | 1 |
| Malignant tumor | 10 (7.8) | 0 (0.0) | 10 (13.0) |
| Epithelial malignancy | 6 | — | 6 |
| Primary ovarian cancer | 3 | — | 3 |
| Stage I | 0 | — | 0 |
| Stage II | 3 | — | 3 |
| Stage III | 0 | — | 0 |
| Stage IV | 2 | — | 2 |
| Primary tubal cancer | 1 | — | 1 |
| Non-epithelial malignancy | 2 | — | 2 |
| Granulosa cell tumor Stage I | 1 | — | 1 |
| Sertoli–Leydig cell tumor Stage I | 1 | — | 1 |

Data are given as n or n (%).
were endometrioma, teratoma, cystadenofibroma and serous cystadenoma, accounting for 61% (63/104) of all benign diagnoses. There were six cases of rare benign abnormality: three Leydig cell tumors and one case each of struma ovarii, steroid cell tumor (as classified by the World Health Organization terminology, 2014\(^{18}\); formerly called stromal luteoma) and stromal hyperplasia with stromal hyperthecosis. Fifteen (12%) patients had a borderline tumor, eight of which were recurrent tumors detected during scheduled follow-up. Eight (6%) patients had an epithelial invasive tumor, including two patients with primary tubal cancer. In addition, two patients had a non-epithelial ovarian malignancy (Sertoli–Leydig cell tumor and granulosa cell tumor).

The diagnoses suggested by the original ultrasound examiners and their level of diagnostic confidence are presented in Table 5. The sensitivity of subjective assessment of ultrasound images for the diagnosis of malignancy was 100% (25/25) and the overall specificity was 86% (89/104). Excluding the unilocular cysts, the specificity was 71% (37/52).

All 10 invasive tumors were correctly classified as malignant by the ultrasound examiner (Table 5), but the specific diagnosis suggested by the examiner was not always correct. One epithelial ovarian cancer was misclassified as a borderline tumor and another as a metastasis to the ovary from endometrial cancer, while two epithelial tubal cancers were misclassified as ovarian cancer (Figures 1 and S1). Two non-epithelial tumors, i.e. one Sertoli–Leydig cell tumor and one granulosa cell tumor, were correctly diagnosed as rare malignancies, and the ultrasound examiner also suggested the correct specific diagnosis (Figure S1).

All 15 borderline tumors were correctly classified as malignant by the ultrasound examiner (Table 5), but one borderline tumor was incorrectly suggested to be a primary invasive epithelial cancer. Images of correctly diagnosed borderline tumors are shown in Figures 2 and S2.

Of the 104 benign lesions, 89 (86%) were correctly classified as benign by the ultrasound examiner, while seven were suspected to be borderline tumors and eight to be invasive tumors. However, the ultrasound examiner was uncertain about malignancy in seven of the 15 misdiagnosed cases (in three of the cases suspected to be borderline tumors and in four of the cases suspected to be invasive tumors). Ultrasound images of serous cystadenomas or cystadenofibromas with papillary...
Figure 1 Grayscale and color/power Doppler ultrasound images of two very small solid invasive malignant tumors. (a,b) Endometrioid ovarian cancer Stage IA synchronous with endometrial carcinoma in asymptomatic premenopausal woman. (c,d) Endometrioid tubal cancer Stage IA in asymptomatic postmenopausal woman. Both tumors were diagnosed correctly as malignancies by ultrasound examiner, but the synchronous ovarian cancer (a,b), diagnosed histologically and immunohistochemically by an expert pathologist, was suggested to be a metastasis to the ovary from endometrial cancer, suspected because of thick irregular endometrium; the tubal cancer (c,d), characterized by rich capsular (arrows) and intralesional perfusion, was suspected to be primary ovarian cancer.

Figure 2 Grayscale (a) and color Doppler (b) ultrasound images of very small serous borderline tumor, diagnosed correctly to be borderline tumor by ultrasound examiner.

projections correctly diagnosed as benign lesions are shown in Figures 3 and S3. Four cystadenomas, one endometrioma, one functional cyst and one Leydig cell tumor were suspected to be borderline tumors. Images of six of the seven benign tumors misclassified as borderline tumors are shown in Figures 4 and S4. Two cases of Leydig cell tumor and one case each of cystadenoma, benign teratoma, struma ovarii, stromal hyperplasia with stromal hyperthecosis, steroid cell tumor, fibroma and fibrothecoma were suspected to be invasive tumors. Ultrasound images of 10 very small benign solid tumors, including six misclassified tumors, are shown in Figures 5 and S5.

Figure 3 Grayscale (a) and power Doppler (b) ultrasound images of very small benign cystadenofibroma with papillary projections, classified correctly as benign tumor by ultrasound examiner. Indication for surgery was clinician’s uncertainty about malignancy. Patient complained of abdominal pressure.

Figure 4 Grayscale (a) and power Doppler (b) ultrasound images of endometrioma suggested incorrectly to be borderline tumor by ultrasound examiner; however, the borderline diagnosis was uncertain.

Figure 5 Grayscale (a) and power Doppler (b) ultrasound images of small solid benign fibroma, detected in premenopausal patient with virilization and suggested to be rare malignancy by ultrasound examiner; however, the malignancy diagnosis was uncertain.

DISCUSSION

In this series of 129 surgically removed adnexal masses with a largest diameter of ≤2.5 cm, 81% of tumors were benign, 12% were borderline malignant and 8% were invasive tumors. The main indication for performing surgery was suspected or possible malignancy in 22% of the benign tumors and in all the malignancies (borderline and invasive). The malignant tumors manifested generally accepted ultrasound signs of malignancy: none was a unilocular cyst, all contained solid components, 80% of the borderline tumors had papillary projections, and all invasive tumors and 80% of the borderline tumors were vascularized on color/power Doppler examination. The sensitivity of subjective assessment of ultrasound images

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with regard to malignancy was 100% and the specificity was 86% (71% if unilocular cysts were excluded). We present a ‘photo gallery’ of correctly and incorrectly diagnosed very small adnexal tumors representative of cases causing diagnostic difficulty.

To the best of our knowledge, this is the first published study describing the ultrasound appearance and corresponding histological diagnosis of surgically removed adnexal masses with a largest diameter of \( \leq 2.5 \text{ cm} \), and also the sensitivity and specificity with regard to malignancy of subjective assessment of ultrasound images of such small masses.

The main limitations of our study are due to its retrospective nature. In particular, some surgically removed very small adnexal masses may not have been included because of failure to identify them, some ultrasound information may be unreliable because it was collected retrospectively from ultrasound images or reports, some ultrasound and clinical information could not be retrieved at all and the main indication for surgery was unclear in 16% of all cases. Another limitation is that the level of expertise of the pathologists was likely to vary between the centers. Moreover, the histological and ultrasound diagnoses were made between 1999 and 2014; during this period, the World Health Organization histopathological terminology was updated and ultrasound technology improved\(^{18}\).

Two prospective multicenter studies have estimated the sensitivity and specificity of various ultrasound methods with regard to predicting malignancy in small adnexal tumors\(^{5,20}\). Ferrazzi \textit{et al.}\(^{20}\) defined a small tumor as one with a mean diameter of \( \leq 5 \text{ cm} \), while Di Legge \textit{et al.}\(^{8}\) defined it as one with a largest diameter of \( < 4 \text{ cm} \). The results of these studies, as well as ours, indicate that it is possible to distinguish small benign adnexal lesions from malignant ones with good accuracy using ultrasonography. However, because of the difference in the study design (retrospective vs prospective) our results are not directly comparable with those of the other two studies, with regard to either the prevalence of different histological diagnoses or the diagnostic performance. Our results are also not comparable with those of Hu \textit{et al.}\(^{21}\), who used qualitative and quantitative analysis of lesion perfusion after intravenous injection of ultrasound contrast to predict malignancy in ovarian cysts with a largest diameter of \( < 4 \text{ cm} \).

It might seem surprising that so many small unilocular cysts with no suspicion of malignancy were surgically removed. Unilocular cysts are associated with a very low risk of malignancy\(^{22}\), while small non-unilocular masses, particularly those with solid components, incur a risk of malignancy and pose a clinical dilemma. The explanation for the surgical removal of the small unilocular cysts is that the decision to operate is taken on the basis of the overall clinical picture. Unfortunately, the indication for surgery was not always clear from the patient records. Latterly a more conservative approach towards managing adnexal masses with benign ultrasound features has been developed. Some of the small unilocular cysts in our study that were removed might have been left \textit{in situ} had they been diagnosed today.

Hillaby \textit{et al.}\(^{16}\) suggested that visualization of apparently normal ovarian tissue in or adjacent to an adnexal mass (ovarian crescent sign) virtually excluded an invasive tumor. Our results show that, if an invasive tumor is very small, normal ovarian tissue can be seen adjacent to it. It is likely that when an invasive tumor in the ovary has reached a size of \( \geq 3-4 \text{ cm} \), most of the normal ovarian tissue has been destroyed, while this is not necessarily the case in smaller tumors (Figures 1 and S1). Also, it is to be expected that a normal ovary will be seen adjacent to a small tubal cancer (Figure 1).

From a clinical perspective, the most interesting part of this work is the collection of ultrasound images provided, especially those of tumors that caused diagnostic difficulty and resulted in an incorrect diagnosis. The difficulty in distinguishing small borderline tumors with papillary projections from small benign cystic lesions with papillary projections can be appreciated from Figures 2 and S2 (borderline tumors), Figures 3 and S3 (benign cystic lesions with papillary projections correctly diagnosed as benign) and Figures 4 and S4 (benign cystic lesions with papillary projections incorrectly suspected to be borderline tumors). The images show that, in agreement with the results presented in Table 2, papillary projections in small borderline tumors tend to be larger and more often vascularized compared with those in benign tumors; however, the overlap in ultrasound appearance between the two categories is also apparent. Shadowing behind papillary projections has been suggested to be a typical ultrasound finding in benign cystadenofibromas\(^{23}\), and this can be seen clearly in some of the benign cystadenomas and cystadenofibromas in Figures S3 and S4. Figures 1, 5, S1 and S5 show overlapping ultrasound features between benign and malignant very small solid tumors. The ultrasound examiner suspected or was uncertain about malignancy in several benign small vascularized solid lesions (fibroma, fibrothecoma, Leydig cell tumor, steroid cell tumor\(^{18}\), stromal hyperplasia with stromal hyperthecosis and struma ovarii). Small endometriomas, dermoid cysts and hydrosalpinges manifested ultrasound features typical of these conditions and usually caused no diagnostic difficulty (except in the case of an endometrioma with papillary projection suspected to be a borderline tumor (Figure 4)). We hope that our gallery of ultrasound images will help examiners discriminate between benign and malignant very small adnexal masses. An image can be more informative than 1000 words!

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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 Ultrasound centers that contributed to the study

Figure S1 Grayscale and power Doppler ultrasound images of four very small solid invasive malignant tumors: one endometrioid ovarian cancer Stage IA synchronous with an endometrial carcinoma, one endometrioid tubal cancer Stage IA, one well differentiated Sertoli–Leydig cell tumor with no heterologous or retiform elements and one granulosa cell tumor. All four tumors were correctly diagnosed as malignancies by the ultrasound examiner, although the type of malignancy was wrongly suspected in two cases.

Figure S2 Grayscale and power or color Doppler ultrasound images of 12 very small borderline tumors: 10 with papillary projections and two solid tumors. All 12 tumors were correctly judged to be borderline tumors by the ultrasound examiner although, in one patient, the ultrasound examiner was uncertain about malignancy.

Figure S3 Grayscale and power Doppler ultrasound images of six very small benign serous cystadenomas or cystadenofibromas with papillary projections correctly classified as benign by the ultrasound examiner.

Figure S4 Grayscale and color/power Doppler images of four benign cystadenomas/cystadenofibromas, one endometrioma and one functional cyst, incorrectly suggested by the ultrasound examiner to be borderline tumors. In three cases the ultrasound examiner was uncertain about the borderline diagnosis.

Figure S5 Grayscale and color/power Doppler ultrasound images of 10 small solid benign tumors: four fibromas, one fibrotheca, two Leydig cell tumors, one steroid cell tumor, one stroma cell hyperplasia with stromal hyperthecosis and one struma ovari. These tumors were misclassified in six cases.

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