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Original Article

Unexpected epithelial ovarian cancers arising from presumed endometrioma: A 10-year retrospective analysis

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ABSTRACT

Objective: To evaluate the incidence and prognosis of unexpected epithelial ovarian cancers (EOCs) occurring in presumed benign endometrioma.
Materials and Methods: Patients who underwent primary surgery at Chang Gung Memorial Hospital between November 2003 and October 2013 were searched with the Systematized Nomenclature of Medicine code followed by chart review.
Results: The incidence of unexpected EOCs in presumed ovarian endometrioma was 0.14%, as 11 patients were revealed after reviewing 497 patients of pathology-proven EOCs in the current series. All patients were aged ≥ 40 years; seven (63.6%) had inward mass within ovarian cyst in preoperative images, six had cancer antigen-125 (CA-125) > 200 U/mL, and two with CA-125 > 1500 U/mL. Ten patients underwent laparoscopy initially, including five with ovarian preservation at the beginning. Ten patients subsequently completed concurrent or secondary staging surgery, including four totally with laparoscopy. The histologic subtypes had clear-cell (8/11), endometrioid (1/11), mixed clear-cell and endometrioid (1/11), and low-grade serous adenocarcinoma (1/11). Seven patients had endometriosis-associated ovarian carcinoma (EAOC), while the other four were non-EAOC with no endometriosis component. The only mortality was a patient of non-EAOC in Stage IIIc, whereas the other 10 in Stage I were alive. The overall survival rate was 90.9% (10/11) with follow-up ranging from 23 months to 130 months.
Conclusion: Unexpected EOCs occurring in presumed ovarian endometrioma was rare and, if present, the prognosis was good in Stage I disease with laparoscopic management. Combining parameters of patient's age, CA-125 level, and inward solid mass at imaging could help to raise the precautions.

Introduction

Endometriosis is one of the most common gynecologic diseases in women of reproductive age, and patients with endometriosis are significantly associated with factors of younger age, nulligravidity, and could have a familial tendency [1,2]. Endometrioma, a specific type of ovarian endometriosis that forms a cystic mass lining with a thin layer of ectopic endometrial tissue and contains chocolate-like fluid content, commonly involves 17–44% of women with endometriosis [3,4].

Endometriosis shares numerous characteristics with invasive cancer, including tissue attachment, invasion, and damage [5,6]. Several studies indicate that women with endometriosis have increased risk of epithelial ovarian cancer (EOC) [5,7,8]. A recent study found that the adjusted hazard ratios of ovarian cancer for Taiwanese women with surgical-confirmed endometriosis was 3.87 compared with those without endometriosis [7], and the adjusted hazard ratios of EOC also consistently increased with age from 3.34 (age < 30 years) to 9.63 (age ≥ 50 years) compared with age-matched Taiwanese women without endometriosis [8]. Epithelial origin is the main category of ovarian cancers and consists of five

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major histological subtypes: clear-cell, endometrioid, mucinous, high-grade serous, and low-grade serous. Each of them shows distinct clinical and pathological characteristics [9]. Specifically, endometriosis-associated ovarian carcinoma (EAOC) is defined as EOC coexisting with endometriosis and bridged with a transitional lesion on the same ovary [10,11]. Numerous studies regarding EAOC have been published, results of which suggest that, in comparison with non-EAOC, EAOC usually develops in younger patients, at an early stage, has better prognosis and associates with specific histological subtypes, namely clear-cell, endometrioid, and low-grade serous adenocarcinoma [9,12,13].

The gold standard of treatment for ovarian endometrioma is operative laparoscopy [14]. Although endometriosis is generally regarded as a benign disorder, malignancy could happen in a presumed ovarian endometrioma with unknown incidence [15]. In literature, the estimates of unexpected malignancy during laparoscopic adnexal surgery is approximately 0.9% of benign appearance cysts of different disease nature preoperatively in the premenopausal group and that raised to 3.0% and 13.3% in postmenopausal women and in cases with suspicious ultrasound pictures, respectively [15,16]. These data could not exactly be applied in preoperative counseling for patients of endometrioma who are usually young and very concerned with fertility reserve. The aim of this study is to evaluate the incidence of EOC encountered in patients with preoperatively presumed endometrioma, the possible risk factors in preoperative evaluation, and to analyze their prognosis with various treatment modalities within a 10-year span in our hospital.

Materials and methods

The study was reviewed and approved by the Human Investigation Review Board of Chang Gung Memorial Hospital. All patients who underwent surgery gave written informed consent.

Patients

We conducted a retrospective study at Chang Gung Memorial Hospital using the Systematized Nomenclature of Medicine code to search for all consecutive patients with a pathologic diagnosis of EOC from November 1, 2003 to October 31, 2013. Patients noted to have cancer metastasizing to the ovary or having primary surgery at other hospitals were excluded. In a further chart review, patients who had preoperatively documented impression of at least borderline ovarian tumor or frank cancer were excluded. (Figure 1)

From the remaining patients with a preoperative impression of benign ovarian mass or uncertain diagnosis of malignancy, those with presumed ovarian endometrioma were found by extensive review of the clinical courses and the preoperative images using the following criteria: (1) premenopausal status; (2) cystic or ground glass content; (3) one to four locules; and (4) no obvious papillations with detectable blood flow [17]. Moreover, patients with findings of tumor diameter > 15 cm or massive ascites above the true pelvis, which highly raise the suspicion of malignancy [18], were also excluded. Two gynecologists were responsible for the review task and assented to the rationale of preoperative impression of endometrioma.

Data and treatment course recording

Patient demographics including age and body mass index (BMI), and the preoperative evaluation including the initial tumor size and the cancer antigen-125 (CA-125) level were recorded, in association with the original reports of the preoperative images and the re-evaluation findings using the above-mentioned criteria.

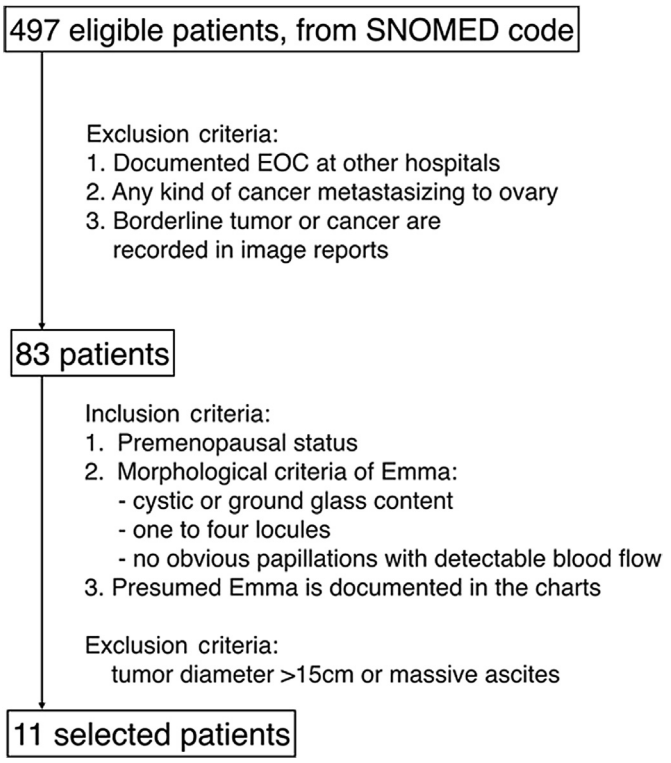

Figure 1. Flowchart of patient selection. Emma = endometrioma; EOC = epithelial ovarian cancer; SNOMED = Systematized Nomenclature of Medicine.

Operations preserving the uterus or either ovary were classified as conservative therapy. Staging procedure consists of peritoneal washing cytology, hysterectomy, bilateral adnexectomy, omentectomy, systemic pelvic, and/or suspicious para-aortic lymph node dissection and excision of any suspicious peritoneal lesions to achieve the level of optimal debulking. Primary staging was defined as the surgery performed immediately after the result of frozen section and secondary staging was that executed on another day no matter the length of interval between the surgeries. For cases in which surgical records mentioned no detail about the integrity of the ovarian masses, the tumors were designated as International Federation of Gynecology and Obstetrics (FIGO) Stage IC. Adjuvant chemotherapy was recommended for cases with Substage IB/C disease or clear cell adenocarcinoma. Paclitaxel and platinum-based regimens (usually cisplatin or carboplatin) of three to six courses were prescribed.

Pathologic reports, including the intraoperative frozen section, were recorded and analyzed. EAOC was defined as coexistence of endometrioma and EOC in the ipsilateral ovary. Histologic classification was performed according to FIGO recommendations [19]. Patient status of follow-up and survival were recorded. For those who did not visit our hospital, we followed them up with a telephone consultation.

Data analysis

Age and BMI were considered as continuous variables and presented as mean ± standard deviation. Incidence was presented as a percentage (%), and range was given where suitable. Descriptive statistics were performed using SPSS for Windows, release 17.0.0/2008 (IBM-SPSS, Inc., Chicago, IL, USA).

Results

Among a total of 497 patients of pathology-proven EOCs in our institutional database, 28 were excluded because of primary surgeries at other hospitals, and 37 were excluded due to pathologic diagnosis of Krukenberg tumor. Another 349 patients had documented preoperative impression of at least borderline tumor or frank ovarian cancer and underwent further surveillance as well as counseling, thus were excluded from the present study (Figure 1).

The remaining 83 were patients of primary EOCs who underwent surgery in our hospital with a somehow uncertain diagnosis of malignancy or presumed benign ovarian tumor preoperatively. By using the criteria mentioned above to re-evaluate the diagnostic images and charts of these patients, 11 of them were finally classified as preoperatively presumed ovarian endometrioma. As there were a total number of 7629 cases of pathology-proven ovarian endometrioma in the same period, the incidence of unexpected EOCs arising from ovarian endometriomas was 0.14% (11/7629) in the present study.

The clinicopathological characteristics of these patients are listed in Table 1. All the 11 patients were aged ≥ 40 years, with the mean age at the time of surgery 44.7 ± 3.4 years (range, 40–52 years). The mean BMI was 22.3 ± 4.2 kg/m^2 (range, 17.5–30.8 kg/m^2). The preoperative CA-125 levels ranged from 18.8 U/mL to 3416 U/mL, with two patients having an extremely high value (1921 U/mL and 3416 U/mL, respectively), and the other four patients ranging from 200 U/mL to 400 U/mL; however, four (36.3%) patients were within the normal limit (≤ 35 U/mL). The preoperative tumor size ranged from 4.4 cm to 15 cm, with three (27.3%) patients having a tumor diameter > 8 cm (10.4 cm, 11.7 cm, and 15 cm, respectively); another five (45.5%) patients had a tumor diameter 5–8 cm; however, three tumors were < 5 cm.

In the re-evaluation of the preoperative images, seven (63.6%) patients of initially presumed ovarian endometrioma were noted with obvious inward soft tissue density within their ovarian cysts, which could have been mistaken as the precipitate of condensed endometrioma (Figure 2). However, the other four patients had images of ovarian cysts that could be acceptable for meeting the above-mentioned criteria of endometrioma (Figure 3). If only these four patients were brought into calculation, the incidence of unexpected malignancy in a presumed ovarian endometrioma was decreased to 0.052% (4/7629) in the premenopausal group. However, two of these four patients had a CA-125 value > 200 U/mL (208.2 U/mL and 1921 U/mL, respectively); another patient did not have the data, and one patient was noted with CA-125 value in the normal limit (34.31 U/mL).

Ten patients underwent surgery via laparoscopic approach initially, of which five had enucleation procedures only at the beginning, which could inevitably lead to intraoperative spillage, and two were carried out in emergency due to rupture of endometrioma before operation (Table 1; Patients 7 and 10). Only one of the 11 patients underwent laparotomy owing to the large size of her tumor (Table 1; Patient 6). Ten patients subsequently completed concurrent or secondary staging surgeries, of which four were carried out totally with laparoscopy.

Seven patients (Table 1; Patients 3, 4, 5, 6, 7, 9, and 10) in the present series revealed suspicious specimen intraoperatively, which were sent for frozen-section examination and revealed malignancy. Four of the patients underwent concurrent staging surgery, of whom three were converted to open and the other one was completed with laparoscopy. The other three received the preliminary diagnoses from frozen section as only borderline tumors (Table 1) and did not undergo staging surgery, of whom two were treated conservatively with ovarian wedge resection (Patient

Table 1
Characteristics of patients with EOC arising from presumed endometrioma ($n = 11$).

Patient	Age (yr)	BMI	OP date	CA-125 (U/mL)	Image report	Tumor size (cm)	Inward mass of cyst[b]	OP Method	Result of frozen	Further surgery	Interval[a]	Pathology	FIGO stage	EOAC or not	Adjuvant C/T	Out- come	Disease-free
1	47	26.2	Aug 2004	—	NS	6.3	No	L's	USO	2°, L's Staging	28 d	CC ADC	IA	No	Yes	Alive	Yes
2	40	18.3	Jan 2007	34.31	Emma	4.4	No	L's	Enu	—		L-G Ser ADC	IC1	No	No	Alive	Unknown[c]
3	40	20.6	Apr 2008	380	Emma	11.7	Yes	L's	USO (f)	Serous ADC		CC ADC	IIIC	No	Yes	Dead	Dead
4	45	21.5	May 2010	3416.4	Emma	7	Yes	L's	USO (f)	ADC		CC ADC	IC2	No	Yes	Alive	Yes
5	44	17.5	Jul 2010	218	Emma	7.6	Yes	L's	Enu (f)	EM BDL tumor		EM ADC	IC1	EAOC	No	Alive	Unknown[c]
6	47	27.4	Aug 2010	326.8	Emma	15	No	Open	USO (f)	1°, Open ATH+BSO		CC ADC	IC1	EAOC	Yes	Alive	Yes
										Emma with atypical cell							
7	43	30.8	Nov 2010	18.8	Emma	4.5	Yes	L's	USO (f)	1°, Open Staging		CC ADC EM ADC	IC2	EAOC	Yes	Alive	Yes
8	43	20.1	Dec 2011	20.6	Emma	6.2	Yes	L's	Enu	—	14 d	CC ADC	IC1	EAOC	Yes	Alive	Yes
9	46	20.6	Feb 2012	208.2	NS	10.4	No	L's	Enu (f)	2°, Open Staging		CC ADC	IC1	EAOC	Yes	Alive	Yes
										1°, L's Wedge							
										Serous BDL tumor							
10	45	23.1	Jul 2013	1921.6	Emma	4.6	No	L's	Enu (f)	high-grade ADC		CC ADC	IC2	EAOC	Yes	Alive	Yes
11	52	19.5	Oct 2013	32.3	Emma	5.9	Yes	L's	USO	—	14 d	CC ADC	IA	EAOC	Yes	Alive	Yes
										2°, Open Staging							

1° = primary staging surgery performed concurrently; 2° = secondary staging surgery performed after an interval period of days.; ADC = adenocarcinoma; ATH = abdominal total hysterectomy; BDL = borderline; CA-125 = cancer antigen-125; C/T = chemotherapy; CC = clear cell; EAOC = endometriosis-associated ovarian carcinoma; EM = endometrioid; Emma = endometrioma; Enu = enucleation of ovarian tumor; EOC = epithelian ovarian cancer; (f) = intraoperative frozen-section examination; FIGO = International Federation of Gynecology and Obstetrics; L's = laparoscopy; L-G S = low-grade serous; NS = nonspecific; OP = operation; Open = laparotomy; USO = unilateral salpingo-oophrectomy; Wedge = wedge resection of ovary.

[a] Interval before the next staging surgery.

[b] To review if suspicious solid mass shadow or papillation was noted within the ovarian cystic lesion in preoperative image.

[c] Lost to follow-up but alive with telephone confirmation.

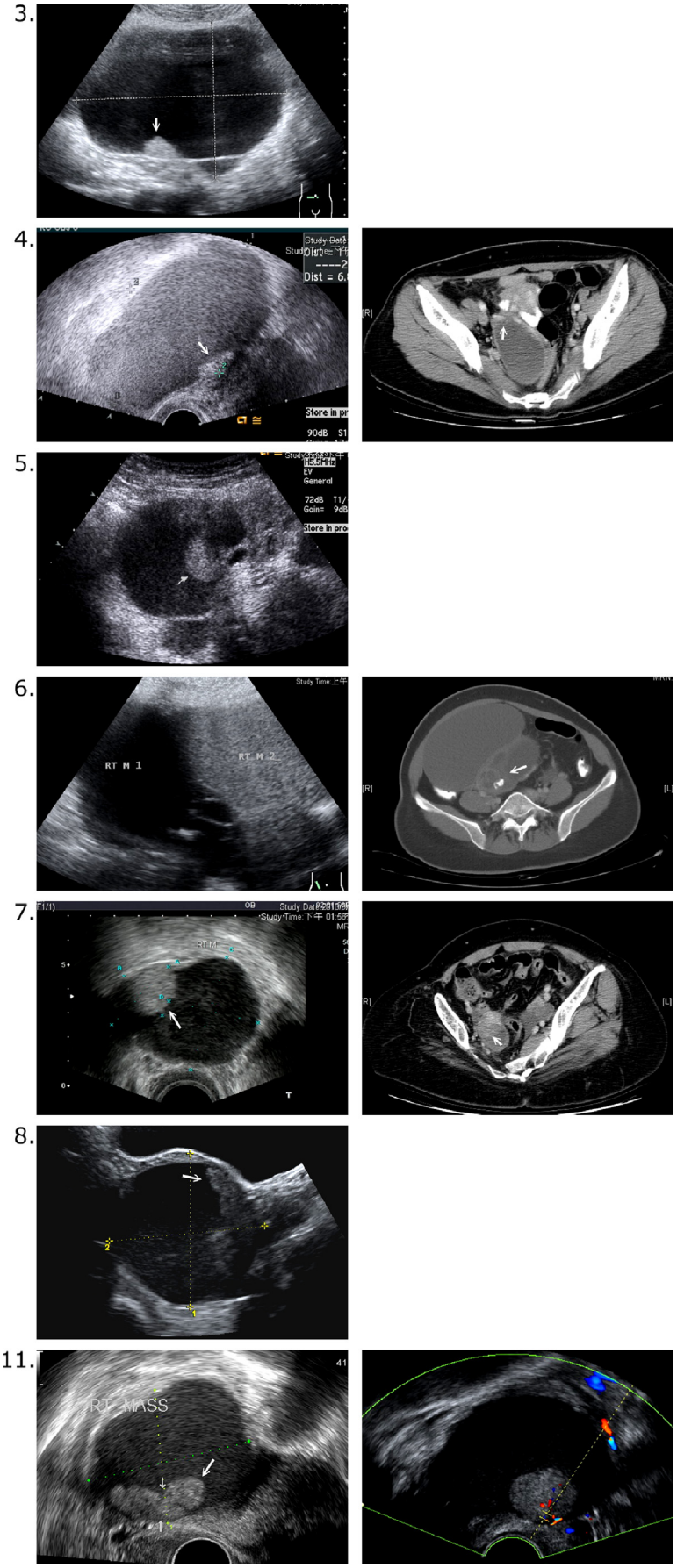

Figure 2. Image analysis of those with suspicious inward mass within cysts or with multiloculated cystic components (white arrow). Patients were numbered as in Table 1. Left column, ultrasonogram; right column, computed tomogram or duplex ultrasonogram.

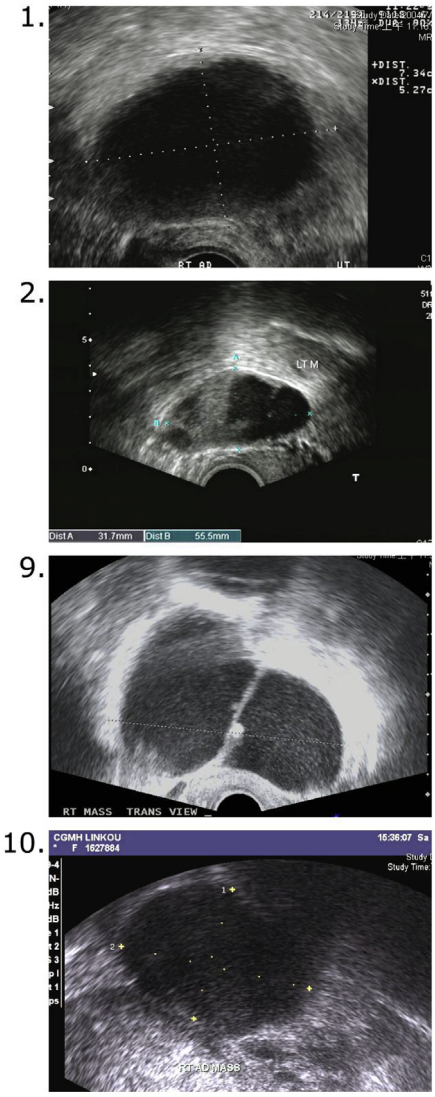

Figure 3. Ultrasonogram of those acceptable to the image criteria of endometrioma. Patients were numbered as in Table 1.

9) or bilateral salpingo-oophorectomy (Patient 5), the other one underwent abdominal hysterectomy and bilateral salpingo-oophorectomy (Patient 6).

The remaining four patients were recognized with ovarian malignancies at the final pathologic report (Table 1; Patients 1, 2, 8 and 11); three of them underwent secondary staging surgery after an interval of 14–28 days with no residual malignancy noted.

Eight patients had clear cell adenocarcinoma, one had endometrioid adenocarcinoma, one had low-grade serous adenocarcinoma, and one had mixed clear cell and endometrioid adenocarcinoma. Four of the 11 were non-EAOCs, in which the pathologist failed to find coexisting endometriosis in the same ovary with EOC. Three of the non-EAOCs patients had adenomyosis or pelvic endometriosis located totally outside the ovarian lesions and in one case, the finding of endometriosis was not mentioned. The remaining seven patients had pathologically-proven EAOCs (Table 1).

Three patients had prior surgical history with pathology-proven endometriosis, and were presumed to have recurrent endometrioma (Table 1; Patient 3, 5, and 7). Two of them proved to have EAOC and the other (Patient 3) had non-EAOC, which was irrelevant to the previous endometriosis operation and which finally led to mortality.

All patients were suggested for adjuvant chemotherapy post-operatively; however, two of the patients (Patients 2 and 5) declined the advice and were also lost to follow-up with uncertain disease status, but were known to be alive at the date of this report (Table 1).

The only mortality in the current series was a patient undergoing primary laparoscopic adnexectomy and concurrent laparotomic staging and debulking surgery. The preoperative ultrasound revealed a right adnexal uniloculated cystic mass with marked inward papillations (Figure 3; Patient 3) that was presumed to be recurrent endometrioma based on pathology-proven endometrioma 9 years previously. Intraoperative frozen section showed ovarian serous adenocarcinoma and peritoneal metastatic adenocarcinoma of FIGO stage IIIC. Final pathology later proved the tumor to be a non-EAOC, which seems irrelevant to its previous ovarian endometriosis. The tumor relapsed and metastasized to the supraclavicular lymph node, and the patient expired 12 months after the surgery, despite having undergone rigorous chemotherapy with paclitaxel and platinum-based agents.

Ten patients with FIGO Stage I survived, eight of whom were kept under regular follow-up and were confirmed to be disease-free to date. The overall survival rate was 90.9% (10/11) in the present series.

Discussion

As ovarian endometrioma is one of the most frequent diseases of conservative laparoscopic surgery [20–23], the present study found the overall incidence of unexpected malignancy arising from presumed ovarian endometrioma was 0.14% in a 10-year span of a single institution. Interestingly, all the patients were aged $\geq$ 40 years. Three of the patients had presumed recurrent ovarian endometrioma with previously proven pathology of benign endometriosis; however, one of them was non-EAOC and had no endometriosis noted on final pathology. If only those without inward soft tissue mass in the presumed ovarian endometrioma were brought into calculation, the incidence could be decreased to 0.052%.

Because of the preoperative impression of benign endometrioma, almost all of the patients (10 of 11) underwent laparoscopic surgery except the one with a large tumor size of 15 cm. Four patients also underwent a further concurrent or subsequent laparoscopic surgery, including two of them for staging surgery. All these patients had good prognosis to the date of this report, although mainly because of the early stage of the disease; however, the laparoscopic approach did not seem to compromise the prognosis of these patients, which was compatible with the findings of other recent studies [15,24–26].

One risk of unexpected malignancy in conservative laparoscopic surgery is the unintended dissemination of cancer cells. Although we do as much as we can to prevent the intraoperative rupture of the cystic tumor [24], it is hard to exclude its occurrence totally in the procedure of ovarian enucleation, especially at the instance of ovarian endometrioma. However, cyst rupture rate for performing total adnexectomy in laparoscopy was low and comparable to laparotomy in tumors < 10 cm [27] and, fortunately, a large proportion of the malignant tumors were < 10 cm [15,28]. Compatibly, in the present study, eight (72.7%) patients of EOC had a tumor diameter < 10 cm. Performing total adnexectomy directly instead of enucleation could prevent a large proportion of intraoperative spillage in patients with suspicion of ovarian malignancies.

However, whether rupture results in a worse prognosis has been another issue of debate for many years [29]. Some studies reported

that tumor rupture prior to or during surgery was associated with poor prognosis [30,31], while some other reports advocate that intraoperative rupture is not a prognostic factor on survival [32–34]. Some investigators have reported that the prognosis was the same in Stage IC even if the standard staging surgery for ovarian cancer was not performed [15,35]. In the present study, 10 patients were Stage IC or higher, four of them did not undergo standard staging surgery, and two of them underwent cystectomy only and preserved the ovary; nevertheless, their prognosis were good. Even though the prognosis seemed optimistic, we still advise that any intraoperative spillage should be prevented if possible.

Although frozen section is currently the most reliable way of reference for intraoperative decision-making, it has limitations. In the present study, three out of the seven patients (42.9%) taking frozen section examination got the diagnosis of borderline tumor initially, which finally turned out to be adenocarcinoma (Table 1). One series, including 141 patients undergoing laparoscopic ovarian surgery, reported that the accurate rate of frozen section was 88.7% [36]. In addition, the frozen section was correct in 75% of malignant tumors, compared with 77.8% of borderline lesions and 95.5% of benign tumors. The surgeon should, therefore, keep in mind the possibility of a more advanced final diagnosis. The choice of fertility preservation and the limitations of frozen section should be well counseled with the patient and her family preoperatively, intraoperatively, and postoperatively.

EOAC is a term with currently no strict definition. Sampson [10] proposed pathologic criteria including: (1) clear evidence of endometriosis should be found close to the tumor; (2) the histopathologic appearance should be such that the origin of the tumor from endometriosis is plausible; and (3) no other primary site should be found. A pooled analysis of case-controlled studies including 23,144 women found that questionnaire-based self-reported, broadly defined, endometriosis were associated with significantly increased risk of clear-cell, endometrioid, and low-grade serous ovarian cancers [9]. Consistent with previous literature, the histological subtypes in the present series were limited to clear-cell (8/11), endometrioid (1/11), mixed clear-cell and endometrioid (1/11), and low-grade serous adenocarcinoma (1/11). Regardless of the existence of soft tissue inward or not, all the presumed endometrioma were not related with high-grade serous or mucinous invasive ovarian cancer or other subtypes of epithelial carcinoma. Histologically, in our study, seven of 11 patients were EAOC, in which the endometriosis and EOC coexisted in the same ovary, and all of these patients survived.

There were several limitations of the present study. First, it was limited by its retrospective design. However, it is hard to investigate the incidence of ovarian cancer arising from ovarian endometriosis prospectively due to the high incidence of endometriosis and the low incidence of ovarian cancer (> 130 vs. < 5.0 per 100,000 women) [37,38]. Because this sort of study is somehow aimed to answer the incidence of preoperatively false-negative diagnosis of ovarian cancer (ovarian cancer mistaken as endometrioma), we designed our study with the starting point of pathology-proven EOC. Thereafter, we underwent pathology, chart, and/or image review with uniform diagnostic criteria to lessen this recall bias. Second, the base of patient collection was limited in a single center. The interobserver and intraobserver bias in the preoperative interpretation could be decreased; however, a multinational, multicenter study could be initiated in the future as a better solution to this weakness [39,40].

In conclusion, the overall incidence of unexpected EOC in a presumed ovarian endometrioma was as low as 0.14%, including the EAOC or non-EAOC, or even presented as a recurrence of proven ovarian endometrioma. Preoperative evaluations on images and tumor markers in the current series varied in a wide spectrum that it actually is impossible to make a reliable preoperative differential diagnosis; however, patients of age > 40 years in association with inward solid prominence in image and/or CA-125 > 200 U/mL should be alert for possible malignancy and given preoperative counseling cautiously. Although almost all patients underwent laparoscopy initially, some of them had preoperatively existed or intraoperatively inevitable tumor spillage, and some underwent subsequent laparoscopic staging surgery, the overall survival was comparatively high (10/11, or 90.9%). Those whose preoperative images had no inward solid mass, and whose postoperative pathology disclosed EAOC, all survived. The only death was a patient of non-EAOC with inward solid mass within cyst and in Stage III disease. While further prospective, larger scale study is needed, we believe the results of the current study could offer some useful reference for reproductive surgeons to deal with patients of presumed ovarian endometrioma.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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H.-H.K. and C.-F.Y. conceived and designed the study; H.-H.K. and C.-Y.H. acquired the data; S.-H.U. reviewed the pathology; H.-H.K. and C.-F.Y. analyzed and interpreted the data; H.-H.K. and C.-Y.H. drafted the manuscript; S.-H.U., K.-G.H., C.-L.L., and C.-F.Y. reviewed the data and revised the manuscript critically for scientific and intellectual content. All authors approved the final version for submission.

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