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Early stage primary ovarian mucinous carcinoma: Outcome-based clinicopathological study in comparison with serous carcinoma

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Abstract

Objective: To compare clinicopathological characteristics and survival rates between patients with primary ovarian mucinous carcinoma and those with primary ovarian serous carcinoma.

Methods: This retrospective study reviewed archival tumour specimens, originally diagnosed as primary ovarian mucinous carcinoma, using refined histological criteria. All patients were contacted to establish survival status. Clinicopathological characteristics and patient survival data were compared with a group of control patients with primary ovarian serous carcinoma.

Results: Of the 33 patients originally diagnosed with primary ovarian mucinous carcinoma, this diagnosis was only confirmed in 18. Primary ovarian mucinous carcinoma was more commonly associated with early International Federation of Gynecology and Obstetrics tumour stages and low-grade histology than primary ovarian serous carcinoma. Patients with primary ovarian mucinous carcinoma had a significantly higher overall 5-year survival rate than those with primary ovarian serous carcinoma (12/12 [100%] versus 14/24 [58%]). Kaplan–Meier survival plots demonstrated that patients with primary ovarian mucinous carcinoma had a survival advantage over patients with primary ovarian serous carcinoma.

Conclusions: Primary ovarian mucinous carcinomas are frequently low-grade, stage I tumours and have an excellent prognosis.

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Introduction

Primary ovarian epithelial carcinoma remains the most lethal gynaecological malignancy to date. For example, in the USA in 2013, ~22 240 cases of ovarian cancer were diagnosed and 14 030 women died from the disease.[1] Of the ovarian epithelial carcinomas, serous carcinoma is the most common histological subtype, accounting for >70% of cases.[2] In addition to serous carcinoma, other uncommon subtypes comprise endometrioid, clear cell, mucinous, mixed, and Brenner (transitional cell) carcinomas, but there are also those with undifferentiated histologies. Research has demonstrated that ovarian mucinous carcinoma has a much lower incidence than that reported for primary ovarian epithelial malignancies.[3] Ovarian mucinous carcinoma also has a distinct biological behaviour and clinical course, compared with serous carcinoma subtypes.[4] Common features of primary ovarian mucinous carcinoma include young age at the time of diagnosis, well-differentiated histology (typically within the unilateral ovary) and rare extraovarian involvement.[5] All of these clinicopathological characteristics suggest that the management of ovarian mucinous carcinoma should be different to that for ovarian serous carcinoma. However, more evidence is required to consolidate these findings.

A major concern associated with ovarian mucinous carcinoma is the fact that metastatic carcinoma is much more common than primary tumours.[6] Metastatic ovarian mucinous carcinomas may originate from the colorectal region, pancreas, biliary tract, appendix, stomach, uterine cervix or other primary sites.[7] The prognosis is substantially different between metastatic and primary ovarian mucinous carcinoma,[7] so the differential diagnosis between these carcinomas becomes a critical issue. Under most circumstances, this distinction can be attained via a combined analysis of pathological and clinical features, but it may be problematic if the extraovarian primary carcinoma is inconspicuous. Consequently, a considerable proportion of ovarian metastatic mucinous carcinomas are misdiagnosed as primary tumours.[7] Accurate diagnosis therefore becomes a precondition for the optional treatment of primary ovarian mucinous carcinoma.

This retrospective study aimed to compare the clinicopathological characteristics of patients with primary ovarian mucinous carcinoma with those of paired control patients with primary ovarian serous carcinoma, using archival materials and data from medical records.

Patients and methods

Patient population

In order to allow for the low incidence of ovarian mucinous carcinoma,[3] this retrospective study analysed surgical specimens and clinical data from all patients originally diagnosed with primary ovarian mucinous carcinoma at the Department of Gynaecological Oncology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China between January 2002 and December 2009. Surgical specimens were retrieved from the Department of Pathology at the Women's Hospital. Histological slides were re-reviewed and rediagnosed by a senior pathologist (B.L.) according to the consensus diagnostic criteria.[3] Pathological parameters were recorded, including histological

grade, tumour growth pattern and vascular space involvement.

Primary ovarian serous carcinoma specimens were retrieved from the Department of Pathology, Women's Hospital, to be used as paired controls (ratio of 2 : 1 between serous and mucinous carcinomas). Serous carcinoma specimens were chosen according to the nearest surgery date from (one before and another after) that of the mucinous carcinoma specimens. Inclusion criteria for this study were: (i) patients underwent their primary surgery in the Women's Hospital; (ii) postoperative chemotherapy was given to patients in whom it was clinically indicated; (iii) patients' clinicopathological records were available.

All patients, including mucinous and serous subtypes, underwent primary staging or cytoreductive surgery; some patients received postoperative platinum-based chemotherapy. For all patients, the following clinical variables were collected from the medical records: patient age; International Federation of Gynecology and Obstetrics (FIGO) stage;[8] tumour location; maximum size of tumour; preoperative serum cancer antigen 125 (CA125) and carcinoembryonic antigen (CEA) levels; volume of ascites and tumour residues after primary surgery. A two-tiered grading system was applied in serous carcinoma cases according to the MD Anderson Cancer Center criteria.[9]

All patients included in the study underwent follow-up interviews in the clinic or via a telephone call to obtain information on patient survival. The deadline for follow-up was 1 May 2013.

The study was approved by the Ethics Committee of The Women's Hospital (reference number: 20120048). Informed patient consent was not required for this study because only routine procedures were used, only information on the cases was collected from the medical records, no additional biological samples were collected from the patients, no confidential patient information was disclosed, and no therapeutic interventions or advice were provided to the patients.

Immunohistochemical analysis

All ovarian mucinous carcinoma surgical specimens were subjected to routine immunohistochemical staining for cytokeratin (CK) 7 and CK20, in order to aid in the differential diagnosis between primary and metastatic ovarian mucinous carcinomas. Tissue samples were fixed in 10% neutral-buffered formalin and embedded in paraffin wax. Specimens were sliced continuously into 4-μm-thick sections, and were stained with haematoxylin and eosin. Slides were reviewed by a senior pathologist (B.L.), and those typical morphology were selected for immunostaining. After the tissue sections had been deparaffinized and rehydrated in a descending series of alcohol dilutions, antigen retrieval was carried out at 95°C for 10 min in 10 mM citrate buffer (pH 6.0) in a microwave oven (220 volts, 760 W; Glanze, Shenzhen, China). Slides were then cooled to room temperature. No blocking was carried out prior to incubation with the primary antibodies. The slides were then incubated with mouse antihuman primary antibodies (CK7: clone OV-TL 12/30, 1 : 100 dilution; CK20: clone KS20.8, 1 : 100 dilution; both from DAKO, Glostrup, Denmark) for 45 min at room temperature, then washed twice for 5 min with 10 mM phosphate-buffered saline (PBS; pH 7.4). The slides were then incubated with the secondary antibody (EnVision+^{TM} System-HRP (DAB) For Use with Mouse Primary Antibodies, K4007, Ready-To-Use; DAKO) for 30 min at room temperature, then washed twice for 5 min with 10 mM PBS (pH 7.4). Immunohistochemical staining was visualized by incubation with 0.5 mg/ml 3-diaminobenzidine tetrachloride (Sigma-Aldrich, St Louis, MO, USA) for 10 min at room temperature and the slides were then counterstained with Mayer's haematoxylin.

Immunohistochemical staining was examined and photographed (at ×50, ×200, and ×400 magnification) using a Leica DM3000 light microscope (Leica Microsystems, Wetzlar, Germany). The percentage of positive cells was semiquantitatively recorded in 10 randomly selected high-power (×400 magnification) fields with a diameter of 4.4 mm for each specimen as 0 (<10%), 1+(11–25%), 2+(26–50%), 3+(51–75%) and 4+(>75%). Diffuse expression was defined as >50% positive cells (at least 3+).

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Comparisons of categorical variables between different groups were analysed using Fisher's exact test (χ^2-test). Kaplan–Meier analysis was used to estimate the probability of overall survival. The univariate log-rank test was used to assess the associations between overall survival and recurrence with potential prognostic factors. The threshold was established at 0.05 (two-tailed). A *P*-value of <0.05 was considered statistically significant for all tests.

Results

A total of 33 patients were originally diagnosed with a primary ovarian mucinous carcinoma between January 2002 and December 2009. Re-review and rediagnosis showed that of these 33 patients, there were 18 primary ovarian mucinous carcinomas, eight borderline tumours, and seven metastatic mucinous carcinomas. The misdiagnosis rate of the originally diagnosed primary ovarian mucinous carcinomas was high (15/33, 45.5%). Primary ovarian mucinous carcinomas accounted for 5.2% (18/346) of all primary ovarian epithelial carcinomas diagnosed at the same institution during the same time period. The 18 patients with primary ovarian mucinous carcinomas had a mean ± SD age of 39.7 ± 15.2 years (range, 22–74 years). Of these 18 patients, 17 were classified as FIGO stage I and one was FIGO stage II.[8]

The 18 primary ovarian mucinous carcinomas were all histopathologically low grade and of the gastrointestinal type. They displayed a variety of gland structures, which commonly exhibited an 'expansile' pattern, characterized by remarkably crowded glandular epithelium with little intervening stroma and interconnected in a confluent or labyrinthine pattern (Figure 1a). A few cases showed the presence of destructive stromal infiltration by malignant mucinous epithelium, which is a key criterion in the traditional definition of mucinous carcinoma. Neoplastic cells usually presented significant nuclear atypia (Figure 1b). Tumours were invariably associated with a typical immunostaining pattern, showing diffuse CK7 positive immunostaining and no or weak CK20 immunostaining (Figures 1c and 1d).

Thirty-six patients with primary ovarian serous carcinoma (mean ± SD age, 52.8 ± 10.7 years {range, 28–77 years]) were selected as paired controls. Four patients were classified having as FIGO stage I, seven as FIGO stage II, 22 as FIGO stage III and three as FIGO stage IV tumours.[8] When compared with primary ovarian serous carcinoma, primary ovarian mucinous carcinoma was more commonly associated with younger age, unilateral involvement of the ovary, unilateral tumour side with >10 cm in size, less-advanced FIGO tumour stage, lower histological grade, higher completion rate of optimal primary surgery, more frequent use of unilateral salpingo-oophorectomy, lower volume of ascites and lower preoperative CA125 levels (all $P < 0.05$) (Table 1).

The median follow-up time was 74 months (range, 37–116 months). During

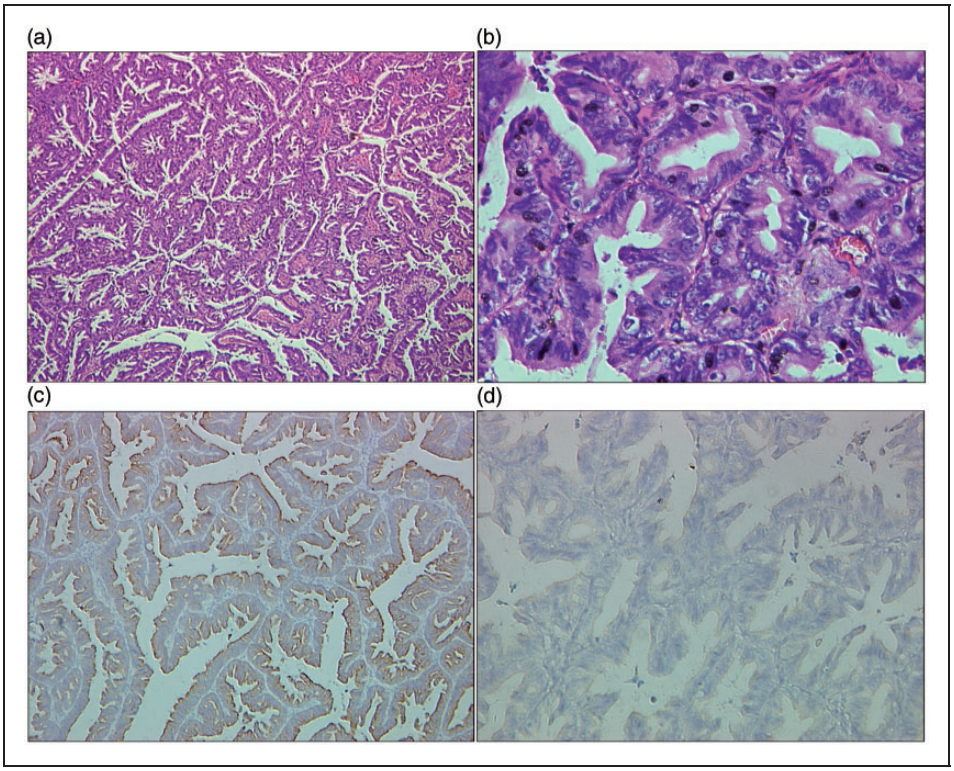

Figure 1. Representative photomicrographs showing the histopathology of a typical primary ovarian mucinous carcinoma specimen. (a) Typical 'expansile' pattern evident in the primary ovarian mucinous carcinoma (counterstained with haematoxylin and eosin [H&E]). (b) Neoplastic cells usually had significant nuclear atypia (counterstained with H&E). (c) Tumours demonstrated diffuse cytokeratin 7-positive immunostaining (counterstained with Mayer's haematoxylin). (d) Tumours were generally negative for cytokeratin 20 immunostaining (counterstained with Mayer's haematoxylin). The colour version of this figure is available at: http://imr.sagepub.com.

the follow-up period, contact was not established with one patient with primary ovarian mucinous carcinoma and one patient with primary ovarian serous carcinoma. All 17 patients with primary ovarian mucinous carcinoma showed no gastrointestinal or other malignant lesions beyond the ovary; all these 17 patients survived with no evidence of recurrence during the follow-up period, although five patients were lost to follow-up within the 5 five years. Therefore, only 12 patients with primary ovarian mucinous carcinomas had 5-year survival data. Among the 17 patients with primary ovarian mucinous carcinoma, four young patients underwent fertility-sparing staging surgery (unilateral salpingo-oophorectomy). In the primary ovarian serous carcinoma group, of the 35 patients available at follow-up, 11 patients were lost to follow-up within the first 5 years, therefore only the remaining 24 patients were included in the 5-year survival analysis. Of these 24 patients with primary ovarian serous carcinoma, 10 died of cancer, so the overall 5-year survival rate was 58.3% (14/24). Women with primary

Table 1. Univariate analysis comparing clinicopathological variables between patients with primary ovarian mucinous carcinoma ($n = 18$) or primary ovarian serous carcinomas ($n = 36$).

Variable	Primary ovarian mucinous carcinomas $n = 18$	Primary ovarian serous carcinomas $n = 36$	χ^2-test	Statistical significance[a]
Age, years				
≤45	13	10	9.694	$P = 0.002$
>45	5	26		
FIGO stage[8]				
I/II	18	11	23.276	$P < 0.001$
III/IV	0	25		
Histological grade				
Low	18	6	33.750	$P < 0.001$
High	0	30		
Type of surgery				
Unilateral salpingo-oophorectomy	4	0	8.640	$P = 0.010$
Cytoreductive surgery	14	36		
Optimal surgery				
Yes	18	26	6.136	$P = 0.021$
No	0	10		
Tumour side				
Unilateral	15	10	14.897	$P < 0.001$
Bilateral	3	26		
Tumour maximum size, cm				
≤10	6	19	1.825	NS
>10	12	17		
Tumour side with >10 cm in size				
Unilateral	10	5	8.191	$P = 0.004$
Bilateral	2	12		
Preoperative CA125 level				
Normal	12	2	23.336	$P < 0.001$
Elevated	6	34		
Preoperative CEA level[b]				
Normal	15	31	2.870	NS
Elevated	3	1		
Volume of ascites, ml				
≤500	17	23	5.834	$P = 0.021$
>500	1	13		
5-year survival[c]				
Alive	12	14	6.923	$P = 0.015$
Died of disease	0	10		

Data presented as *n* patients.

[a]Univariate log-rank test.

[b]Preoperative CEA levels not measured in four patients in primary serous ovarian carcinoma group.

[c]In the primary ovarian mucinous carcinoma group, of 17 patients available at follow-up, five were lost to follow-up within the first 5 years so only the remaining 12 patients were included in the 5-year survival analysis. In the primary ovarian serous carcinoma group, of 35 patients available at follow-up, 11 were lost to follow-up within the first 5 years so only the remaining 24 patients were included in the 5-year survival analysis.

FIGO, International Federation of Gynecology and Obstetrics; CA, cancer antigen; CEA, carcinoembryonic antigen; NS, no significant difference ($P \geq 0.05$).

ovarian mucinous carcinoma showed a significantly higher 5-year survival rate (12/12, 100.0%) compared with women with primary ovarian serous carcinoma ($P = 0.015$). Furthermore, Kaplan–Meier analysis showed that patients with primary ovarian mucinous carcinoma had a survival advantage over those with primary ovarian serous carcinoma ($P = 0.015$; Figure 2) and even over those patients with low-grade serous tumours ($P = 0.014$).

Discussion

The refined diagnostic criteria can result in a shift towards the diagnosis of a borderline mucinous or metastatic mucinous carcinoma rather than primary ovarian mucinous carcinoma.[3,7] Primary ovarian mucinous carcinoma is much less common than previously thought, and probably accounts for only 5% of ovarian mucinous tumours and 3% of ovarian cancers.[10] Most ovarian mucinous carcinomas are therefore metastatic in origin. Consequently, the prognosis of ovarian mucinous carcinoma might be better than that reported one or two decades previously.[5] This present retrospective study provided evidence to support a favourable prognosis in patients with primary ovarian mucinous carcinoma.

The diagnostic standard for distinguishing mucinous carcinoma from borderline tumours lies in the presence of stromal invasion. Two invasive patterns, 'destructive' and 'expansile', have been well recognized in primary ovarian carcinoma. An 'expansile' pattern is the most common pattern in primary ovarian mucinous carcinoma whereas a 'destructive' pattern is less common and should raise the concern for metastatic carcinoma.[11,12] However, the size of the invasive lesion that was sufficient for the diagnosis of mucinous carcinoma varied

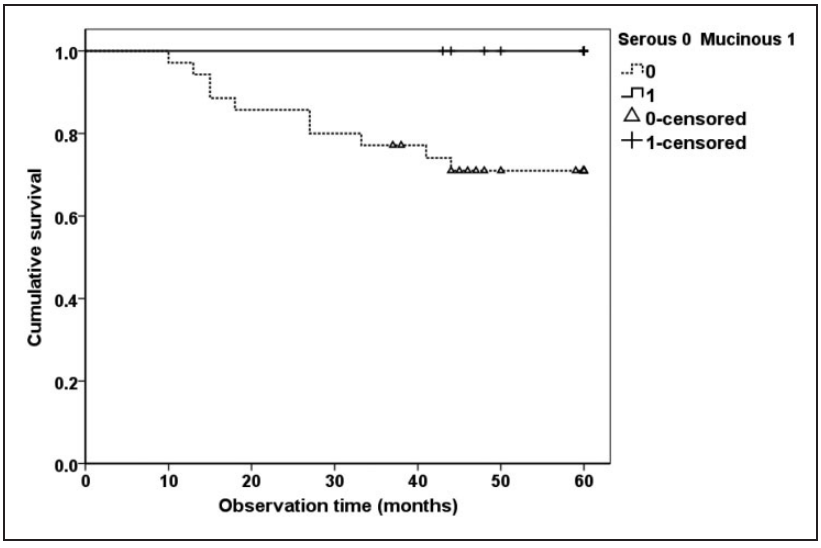

Figure 2. Kaplan–Meier survival plot for patients with primary ovarian mucinous or primary ovarian serous carcinoma. Patients with primary ovarian mucinous carcinoma had a survival advantage over those with primary ovarian serous carcinoma ($P = 0.015$, Log-rank test).

between 2 and 5 mm, and in fact, was not well established.[13] The relatively high proportion of primary ovarian mucinous carcinomas in this present study may be in part associated with the lower diagnostic requirements for the size of the invasive lesion (>3 mm in each of two linear dimensions, World Health Organization 2003 criteria).[14]

The discrimination between metastatic carcinoma subtypes is particularly important since ovarian carcinomas of the gastrointestinal subtype are much more common than those of the endocervical (Mülllerian) subtype.[6] The differential diagnosis between primary and metastatic ovarian mucinous carcinoma has been well established.[12] Primary ovarian mucinous carcinoma commonly has an unilateral, large ovarian lesion (>10 cm) and predominantly presents with an expansile growth pattern, with rare lymphovascular space invasion.[12] Primary ovarian mucinous carcinoma lesions are usually confined to the ovary and the ovarian surface is rarely involved.[4] Metastatic ovarian mucinous carcinoma usually has bilateral, small ovarian lesions (<10 cm) with surface involvement, a nodular growth and haphazard invasion pattern, presence of small glands or tubules and signet-ring cells, and lymphovascular space invasion.[3,7,15,16] The CK7/CK20 immunostaining profile is helpful in the differential diagnosis when the primary tumour is derived from the lower gastrointestinal tract.[17] However, some metastatic mucinous carcinomas (especially those derived from the colorectal region, pancreaticobiliary tract, appendix or endocervix) can share the above features, thus simulating a primary ovarian mucinous cancer.[18] Rarely, the ovarian tumour is the initial manifestation when an extraovarian primary mucinous carcinoma is occult.[7] Clinical evaluation including cancer history, intraoperative exploration, extensive extraovarian spread and follow-up is important for this differential diagnosis. In the current study, metastatic ovarian mucinous carcinoma cases were all rediagnosed on the basis of clinical information, although they morphologically resembled primary ovarian mucinous carcinoma.

The current study found that patients with primary ovarian mucinous carcinoma had a favourable prognosis, whereas those with primary ovarian serous carcinoma (even those with low-grade tumours) had an adverse prognosis. Except for one patient who was not available for follow-up in the primary ovarian mucinous carcinoma group, and five patients lost to follow-up within the first 5 years, the other 12 patients with primary ovarian mucinous carcinoma survived without evidence of relapse during the 5-year follow-up period. These findings suggest that the excellent prognosis in patients with primary ovarian mucinous carcinomas is associated with the predominantly low-grade histology and early tumour stage, as reported previously.[5,19,20] It was reported that the 3-year survival rate for ovarian mucinous carcinoma was 90.0% for stage Ia–Ib, 94.1% for stage Ic, and 100% for stage II tumours.[19] Mucinous carcinomas with an advanced stage are exceedingly rare[10] and the majority are low grade.[5] Research undertaken on mucinous ovarian carcinomas diagnosed between 1988 and 2007 found that the prognosis of advanced-stage mucinous tumours was poor, with a median survival time of 12–33.2 months for stage III–IV tumours; the 3-year and 5-year survival rates were 56.9% and 25.7%, respectively, for stage III tumours.[5] There is increasing recognition that many mucinous ovarian tumours may in fact be metastatic mucinous tumours from other primary sites.[5]

Four young patients with stage I ovarian mucinous carcinoma underwent unilateral salpingo-oophorectomy followed by platinum-based chemotherapy. They were all alive and tumour free during the follow-up period. Currently, staging surgery is the

fundamental option for primary ovarian mucinous carcinoma. Platinum-paclitaxel is the conventional treatment for ovarian mucinous carcinomas although the value of this regimen for true primary ovarian mucinous carcinomas remains uncertain because of classification problems in the published data.[21,22] These current findings suggest that a conservative approach: unilateral salpingo-oophorectomy with chemotherapy might be preferred for women with stage I primary ovarian mucinous carcinoma, especially when fertility conservation becomes a major concern in young women. However, further clinical investigations are required to consolidate this emerging concept, including the possibility of not using subsequent adjuvant chemotherapy in stage I low-grade mucinous tumours.

There were two main limitations in this present study. First, the number of patients with primary ovarian mucinous carcinoma was small and this might be associated with more sampling errors, so could weaken the power of the conclusions. Secondly, the high rate of loss in both groups during the 5-year follow-up period was an important factor affecting the analysis of prognosis, such as the 5-year survival rate.

In conclusion, this present study demonstrated the distinct clinicopathological features of primary ovarian mucinous carcinoma compared with primary ovarian serous carcinoma. These include early tumour stage, low histological grade, common 'expansile' invasive pattern and an indolent clinical course. Based on these findings, we suggest that the intervention for patients with primary ovarian mucinous carcinomas should be different from that used in patients with primary ovarian serous carcinomas, with a shift toward more conservative surgery, especially in young patients where fertility is an issue. Pathologists and gynaecologists should be alert to the prerequisite for the differential diagnosis between primary and metastatic ovarian mucinous carcinoma when making treatment decisions and estimating prognoses.

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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