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Appendiceal mucinous neoplasm mimics ovarian tumors: Challenges for preoperative and intraoperative diagnosis and clinical implication

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ABSTRACT

Objective: The aim of this study was to investigate the clinicopathological characteristics of appendiceal mucinous neoplasm that had been preoperatively misdiagnosed as a mucinous ovarian tumor and to discuss the clinical impacts of misdiagnosis.

Methods: Seventy-eight patients with a final pathologic diagnosis of appendiceal mucinous neoplasm during a 10-year period were retrospectively reviewed. All patients were diagnosed with ovarian tumor before treatment. A univariate analysis was performed to evaluate predictors of the diagnostic accuracy of a frozen section.

Results: The patients' median age was 61 years (range, 21–82 years), and most were diagnosed as low-grade appendiceal mucinous neoplasm (LAMN) (84.62%). The diagnostic concordance between the frozen section and the final pathology was 56.92%. The most consistent diagnosis was LAMN (64.14%). Univariate analysis indicated that maximal diameter of the ovarian tumor (unilateral), laterality of the ovarian tumors (unilateral or bilateral), and frozen section site (appendix or extra-appendix) significantly correlated with the accuracy of frozen section diagnosis (all $p < 0.05$). Although the diagnostic discordance between the frozen section and the final pathology was 43.08%, only one patient was clinically impacted because of suboptimal surgery.

Conclusion: Appendiceal mucinous neoplasm should be considered as a differential diagnosis of pelvic mass in women. For patients who do not require fertility-sparing surgery, excision and frozen section of the bilateral ovaries and appendix regardless of the appearance of the appendix might improve the diagnosis. For older patients with peritoneal dissemination, appropriate cytoreductive surgery is recommended to reduce the clinical impact of misdiagnosis.

1. Introduction

With recent increase in our understanding of the biology of mucinous epithelial ovarian cancer (mEOC) and the application of improved histopathological techniques, the recognition and diagnosis of the mEOC remarkably changed. Epithelial ovarian tumors are classified as benign, borderline, or malignant; and can be further classified as invasive or noninvasive [1]. Ovarian "borderline" mucinous tumors associated with pseudomyxoma peritonei (PMP) and widely disseminated mucinous carcinomas are no longer diagnosed [2]. The reported incidence of mEOC has historically ranged from 7% to 14% [3,4]; however, increasingly, more studies are suggesting that most mucinous ovarian cancers were metastatic, and the incidence of primary mEOC is approximately 3% [5,6]. The primary sites of secondary ovarian mucinous tumors are colorectum, appendix, pancreaticobiliary tract, small intestine, stomach, endocervix, and breast [5,7]. The gastrointestinal (GI) tract is the most common origin.

The incidence of primary appendiceal mucinous neoplasm is approximately 0.5% among all GI tumors, and preoperative diagnosis is difficult [8]. In the past decades, the histological terminology, diagnosis, classification, and treatment of appendiceal neoplasm have been lacking in uniformity, resulting in unclear clinical management. A more thorough understanding of

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appendiceal mucinous neoplasm is currently being strongly promoted. The relationship of this neoplasm with PMP syndrome is also well understood. PMP is a clinical term describing the presence of a mucinous neoplasm within the pelvis and abdominal cavity [2]. It was first considered to be a disease related to the appendix or ovary or a primary disease in the peritoneum [9], but it is now clear that PMP generally originates from a mucinous neoplasm of the appendix [10] and, occasionally, from other organs such as the ovary, colon, pancreas, or urachus [11–14].

A correct preoperative diagnosis is very difficult for gynecologists to establish because specific tumor biomarkers are lacking and appendiceal neoplasms are usually metastatic to the ovary mimicking ovarian tumors. Mucinous borderline ovarian tumors (mBOTs) are subclassified into the GI type (85%–90%) and endocervical-like tumors [2]. Additionally, the intestinal type is the most common subtype of mEOC [1]. Therefore, although the histological criteria and terminology of both appendiceal and ovarian mucinous tumors appear to be well established and standardized, distinguishing mucinous appendiceal neoplasm from primary ovarian mucinous tumors remains a diagnostic challenge for gynecologists and pathologists, especially when using intraoperative frozen section.

A correct diagnosis, especially an intraoperative diagnosis, is important for adequate treatment. In the present study, we investigated the clinicopathological characteristics of mucinous appendiceal neoplasm that had been preoperatively misdiagnosed as a mucinous ovarian tumor, and we discuss the clinical impacts of misdiagnosis.

Materials and methods

Patients and surgical procedures

We retrospectively reviewed all patients who were diagnosed with ovarian tumors and underwent primary surgery at the Department of Gynecologic Oncology of (GYN), Fudan University Shanghai Cancer Center (FUSCC), during a 10-year study period from 2008/01/01 to 2018/09/31. Patients with a final pathologic diagnosis of appendiceal mucinous neoplasm were identified and included in this study. Patients who underwent consultations, had an indeterminate primary site, and had a pathological diagnosis before primary surgery were excluded. The medical records, including physical examination notes, operation records, and pathological data, were carefully reviewed. Operation records were reviewed for information regarding the type of surgery, tumor laterality, presence of ascites, and appearance of the appendix. Cytoreductive surgery (CRS) was pioneered by Sugarbaker with the aim to clear all visible macroscopic diseases from the peritoneal cavity to achieve local disease control [15]. Optimal and suboptimal CRS is commonly performed in patients with ovarian cancer to assess the maximum size of the residual tumor. Optimal CRS means that the maximum size of residual tumor is less than 1 cm. Suboptimal CRS means that the maximum size of the residual tumor is larger than 1 cm. Approval for review of the patients' medical records and pathology reports was obtained from the institutional review board of FUSCC, Shanghai, China.

Frozen section and pathological examination

At the time of frozen section, the sections were frozen, sectioned, stained, and interpreted by the pathologist. Staining of one or more sections was performed depending on the degree of suspicion and tumor size. For permanent sections, immunohistochemical staining was applied in selected cases for suspicious origination. Mucins 2 and 5A, villin, CDX2, PAX8, cytokeratins 20 and 7, estrogen receptor, progesterone receptor, carcinoembryonic antigen (CEA), and cancer antigen 125 (CA125) were the most commonly used markers.

All frozen sections and permanent sections were reviewed by two pathologists and classified and diagnosed based on the World Health Organization classification and Peritoneal Surface Oncology Group international consensus classification [16]. A third pathologist was invited to view the sections to check whether there were differences in the diagnosis between the two pathologists in such cases. We adopted the diagnosis of the third pathologist. The following data were collected from both frozen and permanent sections: site of the frozen section (appendix or extra-appendix), laterality of ovarian tumors (unilateral or bilateral), maximal diameter of the ovarian tumors (unilateral) [17], diagnosis, presence of extra-appendix mucus deposits, and appearance of the appendix.

Statistical analysis

A univariate analysis was performed for factor analysis of the accuracy of the frozen section. The following factors were analyzed: age ($\leq$45 or >45 years), menstrual status, maximal tumor size (unilateral; <10, or $\geq$10 cm) [5], tumor laterality (unilateral or bilateral), site of the frozen section (appendix or extra-appendix), presence of extra-appendix mucus deposits, and appearance of the appendix. A p value of less than 0.05 was considered statistically significant. MedCalc version 11.1.2.0 (MedCalc Software, Ostend, Belgium) was applied for all statistical analyses.

Results

Clinical characteristics of misdiagnosed patients

The data of 78 patients were reviewed. All patients were initially diagnosed with ovarian tumor and underwent primary surgery in the Department of Gynecologic Oncology in FUSCC. The clinical characteristics of all 78 patients are presented in Table 1. The median age of all patients was 61 years (range, 21–82 years). Most patients experienced one or more symptoms before treatment, including pain (32.05%), abdominal distention (61.54%), and weight loss (19.23%). No patient developed an intestinal obstruction. In total, 76.92% of the patients were postmenopausal. The median levels of the tumor biomarkers CA125, CEA, carbohydrate antigen 19–9 (CA19-9), and human epididymis protein 4 were 52.23 U/ml, 20.38 ng/ml, 39.5U/ml, and 70.4 pmol/l, respectively. In total, 58.97% of the patients underwent GI endoscopy before surgery, and no evidence of malignancy was found. In the final pathologic examination, most patients were diagnosed with low-grade appendiceal mucinous neoplasm (LAMN; 84.62%), and the second most common diagnosis was mucinous adenocarcinoma (11.54%).

Comparison of frozen and final diagnoses in different types of appendiceal mucinous neoplasms

The frozen sections of 13 patients were not suitable for review again due to the poor quality; thus, 65 patients were finally reviewed, including 53 patients with LAMN, 9 with appendiceal mucinous adenocarcinoma, and 3 with appendiceal mucinous adenocarcinoma with signet ring cells (SRC). The distribution of the frozen diagnosis compared with the final pathology is shown in Fig. 1. The diagnostic concordance between frozen section and final pathology was 56.92% (37/65). The most consistent diagnosis was LAMN (34/53, 64.14%). Of the 19 discordant cases with a final diagnosis of LAMN, the frozen diagnosis was benign ovarian mucinous tumor (BOMT) (10/19), ovarian borderline epithelial

Table 1
Clinical characters of misdiagnosed appendiceal mucinous neoplasm.

Clinical characters of misdiagnosed appendiceal mucinous neoplasm	
Age(years)	
range	21 to 82
median	61
Symptoms	
pain	32.05% (25/78)
abdominal distention	61.54% (48/78)
weight loss	19.23% (15/78)
intestinal obstruction	0% (0/78)
Menstrual status	
postmenopausal	76.92% (60/78)
premenopausal	23.07% (18/78)
Tumor biomarker (median)	
CA125(0–35 U/ml)	52.23 (3.2–849.4)
CEA(0–5.2 ng/ml)	20.38 (0.86->1000)
CA199(0–35 U/ml)	39.5 (1.21–800.5)
HE4(0–72 pmol/L)	70.4 (36.5–222.54)
Preoperative gastrointestinal endoscopy	
done	58.97% (46/78)
not done/NA	41.03% (32/78)
Pathology type	
LAMN	84.62% (66/78)
mucinous adenocarcinoma	11.54% (9/78)
Mucinous adenocarcinoma with signet ring cells	3.85% (3/78)
Mucinous signet ring cell carcinoma	0% (0/78)
NA not available; CA125, Carbohydrate antigen 125; CEA,carcinoembryonic antigen; CA199, carcinoembryonic antigen	

tumor (7/10), appendiceal mucinous adenocarcinoma (1/19), and ovarian adenocarcinoma (1/19). Of the nine cases finally diagnosed as an appendiceal mucinous adenocarcinoma, only two were correctly diagnosed on the basis of frozen section, five cases were diagnosed with ovarian adenocarcinoma, and two were diagnosed with LAMN. Of the three cases finally diagnosed as appendiceal mucinous adenocarcinoma with SRC, only one was correctly diagnosed; another was diagnosed with ovarian adenocarcinoma, and the last one was diagnosed as metastatic ovarian carcinoma. Data of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of diagnosis by frozen section for the different types of appendiceal mucinous neoplasm are shown in Table 2. For LAMN, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 64.15%, 83.33%, 94.44%, 34.48%, and 67.69%, respectively.

Univariate analysis of predictors of discordance

The following potential predictors of diagnostic discordance were evaluated: age, menstrual status, maximal diameter of the ovarian tumors (unilateral), laterality of the ovarian tumors (unilateral or bilateral), site of frozen section, presence of extra-appendiceal mucus deposits, and appearance of the appendix (Table 3). The univariate analysis indicated that the maximal diameter of the ovarian tumors (unilateral), laterality of the ovarian tumors, and site of frozen section significantly correlated with the accuracy of frozen diagnosis (all $p < 0.05$).

Clinical implications of challenges in the diagnosis of frozen section

Sixty patients underwent optimal CRS, and five patients underwent suboptimal CRS. Among the five patients who underwent suboptimal CRS, four were correctly diagnosed with LAMN during surgery, and only one was misdiagnosed as ovarian adenocarcinoma. Suboptimal CRS was performed on the misdiagnosed patient and one of the correctly diagnosed patients because the tumors could not be removed surgically. All of the other three correctly diagnosed patients were young (<35 years) and declined removal of the ovaries; therefore, they underwent oophorocystectomy. Although the diagnostic discordance between the frozen section and final pathology was 43.08% (28/65), only one patient was clinically impacted because of the suboptimal surgery.

Discussion

Mucinous appendiceal neoplasm is a rare disease with heterogeneous clinical features. The propensity of appendiceal mucinous neoplasm to involve the ovaries is well established. Ovarian metastases were reportedly found in 58.1% of patients with appendiceal neoplasm, and patients with one macroscopically abnormal ovary had a 48.6% risk of involvement of the contralateral ovary. In patients with two macroscopically normal ovaries, 18.2% had microscopic ovarian metastases [18]. Because of the relationship of this neoplasm to PMP syndrome, which is a clinical syndrome characterized by grossly evident, diffuse, intra-abdominal mucinous ascites involving the peritoneal surfaces [16], gynecologic oncologists often encounter mucinous appendiceal neoplasm in patients with intra-abdominal mass and ascites. Because the treatment differs, the ability to correctly diagnose a primary ovarian tumor versus appendiceal neoplasm is critical. Although ultrasound [19], magnetic resonance imaging (MRI), and computed tomography (CT) [20–22] can help to distinguish appendiceal and primary ovarian tumors, a primary mucinous appendiceal neoplasm is rarely diagnosed before surgery compared with other more common diseases [23]. The lack of specific tumor biomarkers for identification is another reason for misdiagnosis. CEA, CA19-9, and CA125 are commonly used tumor biomarkers for both GI- and ovarian-origin tumors. In one study of patients with PMP, the positive rates of preoperative tumor markers were 72.0% for CA125, 47.4% for CA19-9, and 84.6% for CEA [24]. In the present study, the preoperative tumor makers were elevated in most cases; this might have been because most of the patients had peritoneal dissemination (52/65). However, most studies utilize CA19-9 and CA125 as markers for moderating recurrence [25] and predicting prognosis [26], not for diagnosis [27]. Therefore, more specific tumor biomarkers need to be investigated.

We reviewed 78 women with a median age of 61 years, which is similar to the reported age of approximately 60 years [5]. A total of 58.97% of patients underwent preoperative GI endoscopy to exclude GI metastatic tumors, and no evidence of malignancy was found. Unlike for colorectal and GI tumors, GI endoscopy provides little diagnostic information for appendiceal neoplasm. Because preoperative diagnosis is difficult, intraoperative frozen section is important for achieving the correct diagnosis. The diagnostic concordance between the frozen section and final pathology was 56.92%. Among patients with a final diagnosis of LAMN, the most commonly misdiagnosed pathology was a benign ovarian tumor and mBOT. GI-type mBOTs have histological features similar to those of primary mucinous appendiceal neoplasm, and the two conditions can be difficult to distinguish. Therefore, most pathologists maintain that diagnosis of primary mucinous ovarian tumors requires consideration and exclusion of metastases from other GI tumors [1,28–30]. Although SRC carcinoma is always correctly diagnosed intraoperatively, only one in three patients were correctly diagnosed in our study. This might have occurred because of the limited sampling; all of these patients had mucinous adenocarcinoma with SRC (with SRC less than 50%) [16].

The univariate analysis of predictors of discordance showed that the maximal diameter of the ovarian tumors (unilateral), laterality of the ovarian tumors, and site of frozen section were significantly correlated with the accuracy of frozen diagnosis. Seidman et al. [5] established an algorithm for distinguishing primary and metastatic

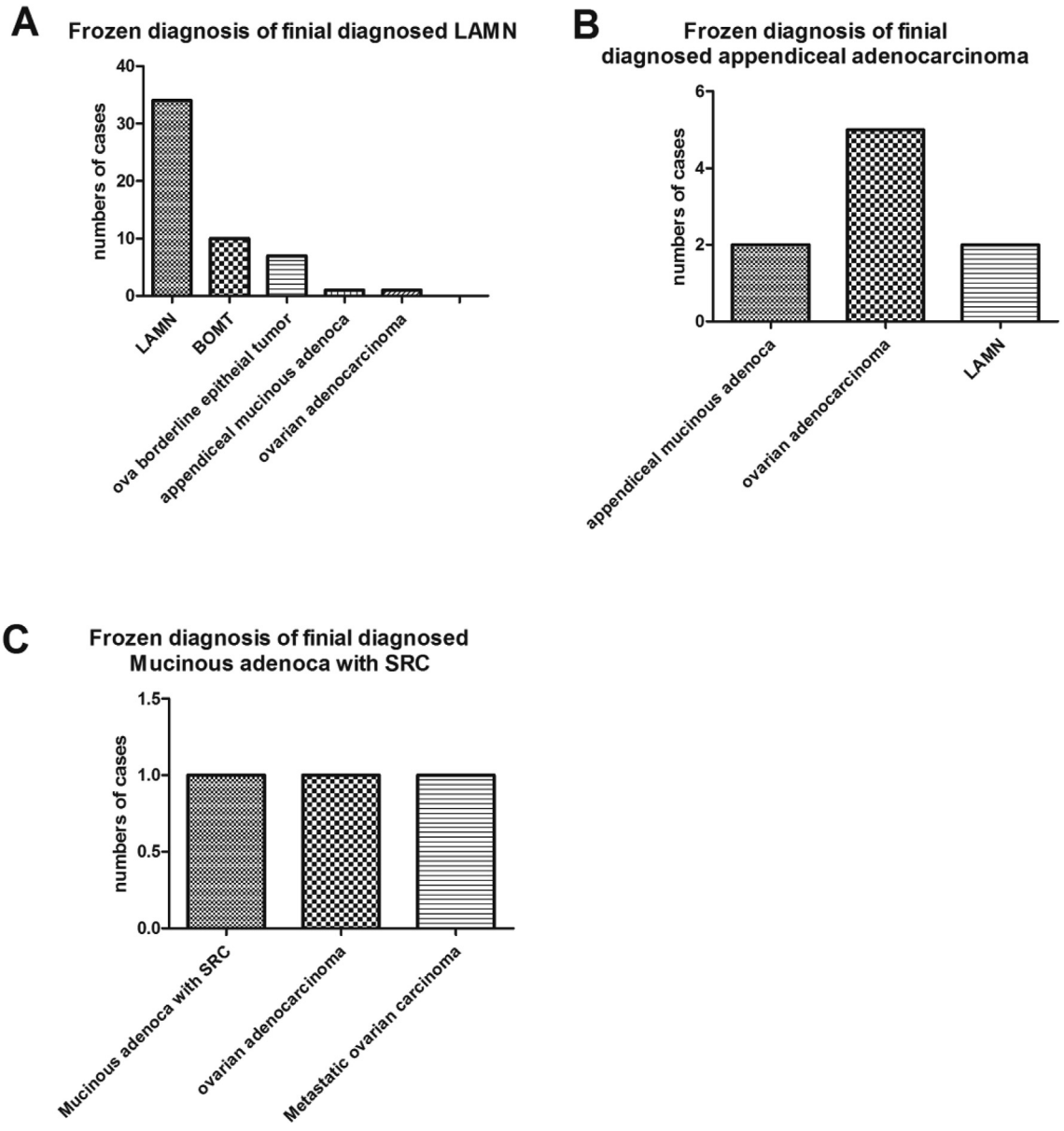

Fig. 1. Distributions of frozen diagnosis compared with final pathology.
LAMN, low-grade appendiceal mucinous neoplasm; BOMT, benign ovarian mucinous tumor; ova borderline epithelial tumor, ovarian borderline epithelial tumor; appendiceal mucinous adenoca, appendiceal mucinous adenocarcinoma; mucinous adenoca with SRC, mucinous adenocarcinoma with signet ring cell.

Table 2
Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of diagnosis on frozen section for different types of appendiceal mucinous neoplasm.

Diagnosis on frozen section	sensitivity	specificity	PPV	NPV	accuracy
LAMN	64.15%	83.33%	94.44%	34.48%	67.69%
appendiceal mucinous adenocarcinoma	22.22%	98.21%	66.67%	88.71%	87.67%
Mucinous adenocarcinoma with signet ring cells	33.33%	100%	100%	96.88%	96.92%

mucinous carcinomas in the ovary, and this algorithm can be used at the time of intraoperative consultation to guide surgical management. Some studies have further assessed the utility of this algorithm [7,17,31,32]. Although most of them were based on the final pathological diagnosis, which might not reflect the exact performance of intraoperative assessment, the results can be translated to intraoperative use with only occasional exceptions [7]. Based on this, we divided the unilateral ovarian tumor size into <10 or ≥10 cm. Interestingly, all <10 cm tumors were correctly diagnosed, while only one patient with a ≥10 cm tumor was correctly diagnosed; this further confirms the utility of the algorithm. However, the utility of tumor laterality to identify metastasis was poorer than

Table 3
Univariate analysis of predictors of discordance.

Factors	Frozen diagnosis compare with final diagnosis		
	Correct diagnosis	Inconsistent diagnosis	P value
Age			0.388
≤45	7	1	
>45	30	27	
Menstrual status			0.559
postmenopausal	24	24	
premenopausal	13	4	
Size (unilateral)*			0.004
≥10 cm	1	4	
<10 cm	5	0	
Side**			0.003
unilateral	7	5	
bilateral	16	20	
Site of frozen section			<0.001
appendix	30	5	
extra appendix	7	23	
Peritoneal dissemination			0.806
presence	30	22	
absence	7	6	
Appendix appearance			0.085
normal	1	4	
abnormal	36	24	

*note: Totally 12 cases were unilateral, exact tumor size only obtained from 10 cases.
**note: totally 9 cases were pathologically confirmed without ovary and fallopian tube involvement, and 8 cases didn't remove bilateral ovary and fallopian tubes (2 cases only removed unilateral, and were confirmed with involvement).

that of tumor size in our study, which might have been because, although 36 patients were finally confirmed to have bilateral metastasis, frozen section was performed on 35 appendiceal sites and 30 extra-appendiceal sites. Thus, not all of the removed bilateral ovarian tumors were checked on frozen section. This indicates that surgeons should provide more information about the patients' clinical features to the pathologist; this might help the pathologist to achieve a correct diagnosis. We also found that the site of frozen section was significantly associated with the correct diagnosis. Frozen section performed on the appendix is more accurate than that performed on extra-appendiceal organs. Additionally, neither the presence of PMP nor the appearance of the appendix influenced the frozen section diagnosis. Although the appendix appeared abnormal in 60 patients, frozen sections were performed on the appendix in only 35 patients. Based on our results, we suggest that in patients with a mucinous ovarian neoplasm, excision and frozen section of the appendix might improve the diagnosis regardless of the appearance of the appendix.

Because the correct intraoperative diagnosis is critical for surgical treatment, we also investigated the clinical impact of misdiagnosis. Among the 37 correctly diagnosed patients, optimal CRS was performed in 33 and suboptimal CRS was performed in 4. Among the 28 misdiagnosed patients, 27 underwent optimal CRS and 1 underwent suboptimal CRS. There was no significant difference in the surgical procedure between the correctly diagnosed patients and misdiagnosed patients. Suboptimal CRS is mostly due to young patients' wish to preserve their fertility; another common reason is the presence of an unresectable tumor. Above all, although the preoperative and intraoperative diagnoses of primary mucinous appendiceal neoplasm are challenging, the clinical impact of surgical treatment is small. This might be because the treatment is the same for both mucinous appendiceal neoplasm and ovarian cancer. CRS is recommended for both appendiceal neoplasm and ovarian cancer [1,33]. In our study, 87.69% of our patients were >45 years old and had no requirement to preserve their fertility, and 80% of patients had peritoneal dissemination; all of these patients underwent appropriate surgical treatment.

The major limitation of our study is the retrospective nature of the clinical data and the single-center design. Our center is the largest ovarian cancer diagnosis and treatment center in East China, and all of our surgeons are skilled in CRS for ovarian cancer, especially in upper abdominal surgery; this makes our surgical treatment more uniform. However, our results do not necessarily reflect the performance of other centers. Another limitation is that we did not perform a multivariate analysis of the predictors of discordance because of the small sample size.

Conclusion

Distinguishing mucinous appendiceal neoplasm from a mucinous ovarian tumor is difficult both preoperatively and intraoperatively. Mucinous appendiceal neoplasm should be considered as a differential diagnosis of a pelvic mass in female patients. For postmenopausal patients, excision and frozen section of the bilateral ovaries and appendix might improve the diagnosis regardless of the appearance of the appendix. For premenopausal patients, adequate preoperative informed consent should be obtained after providing and explanation of the risks and benefits of excision or preservation of the ovaries. For older patients with peritoneal dissemination, appropriate CRS is recommended to reduce the clinical impact of misdiagnosis.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution, and written consent was obtained.

Consent for publication

All of the authors verbally agreed to publish.

Availability of data and materials

The datasets supporting the conclusions of this article are included in the article.

Competing interests

The author(s) declare no competing interests.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.08.004.

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