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Prevalence of Appendiceal Pathology in Ovarian Cancer When Appendectomy is performed during Surgical Treatment

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ABSTRACT

Objectives: Pathological appendectomy findings during the surgical staging procedure for ovarian cancer can determine the extent of the cancer, and specific treatment depends on whether a primary appendiceal malignancy or an ovarian metastasis is involved. This study aimed to evaluate appendiceal histology from comprehensive surgery for epithelium ovarian cancer.

Materials and Methods: We retrospectively evaluated patients who underwent cytoreductive surgery for primary and secondary epithelium ovarian cancer and who had undergone an appendectomy between 2003 and 2016. The clinicopathologic findings concerning ovarian cancer and the appendix, and risk factors for appendiceal abnormalities were presented.

Results: Of 340 patients with ovarian cancers, 322 (94.7%) were diagnosed with primary epithelium ovarian cancer and 60.6% were at an early stage. Mucinous carcinoma was the most common in histology (40%). Appendiceal malignancies were identified in 53 (15.6%) patients, of whom 42 (12.4%) had secondary metastasis from ovarian cancer, and two patients had stomach or breast metastases. Primary appendiceal neoplasms were identified in nine patients, with three patients presenting with synchronous ovarian cancers. A grossly abnormal appendix (odds ratio [OR] 27.6, 95% confidence interval [CI] 7.1–107.3, $p < 0.001$), advanced stage ovarian cancer (OR 114.6, 95%CI 14.6-99.4, $p < 0.001$), and secondary ovarian cancer (OR 86.7, 95%CI 8.5-887.7, $p < 0.001$) were associated with appendiceal neoplasm in multiple logistic regression analysis.

Conclusion: Appendiceal neoplasm accompanied a significant number of ovarian cancers. Appendectomy is recommended as part of surgical staging in abnormal looking appendices, advanced ovarian cancer, and secondary ovarian cancer.

Keywords: appendectomy, appendix, ovarian cancer, pathology.

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พยาธิสภาพของไส้ติ่งในผู้ป่วยมะเร็งเยื่อบุผิวรังไข่ที่ได้รับการตัดไส้ติ่งในขณะผ่าตัดมะเร็งรังไข่

อรุณธร พิเชฐชัยยุทธ์, รักชาย บุหงาชาติ, กรัณฑรัตน์ ปิยนันท์จรัสศรี, ศรันญา วัฒนกำธรกุล, ยุทธศักดิ์ ศุภสินธุ์, สาธนา บุณยพิพัฒน์, คณิตา กายะสุต, อดิศร ชัยกิจ

บทคัดย่อ

วัตถุประสงค์: *พยาธิวิทยาของไส้ติ่งที่ได้จากการตัดไส้ติ่งในระหว่างการผ่าตัดรักษามะเร็งเยื่อบุผิวรังไข่สามารถระบุความกว้างไกลของการแพร่กระจายของมะเร็งรังไข่ได้ ซึ่งการรักษาเพิ่มเติมก็ขึ้นกับว่ามะเร็งที่อยู่ที่ไส้ติ่งนั้นเป็นมะเร็งปฐมภูมิที่ไส้ติ่งเองหรือเกิดจากการแพร่กระจายมาจากมะเร็งเยื่อบุผิวรังไข่ การศึกษานี้มีวัตถุประสงค์เพื่อประเมินผลทางพยาธิวิทยาของไส้ติ่งที่ได้จากการผ่าตัดรักษามะเร็งรังไข่ชนิดเยื่อบุผิว*

วัสดุและวิธีการ: *เป็นการศึกษาจากข้อมูลย้อนหลังในผู้ป่วยที่ได้รับการผ่าตัดรักษามะเร็งรังไข่ชนิดเยื่อบุผิวหรือลุกลามมาจากมะเร็งของอวัยวะอื่นของร่างกาย ร่วมกับการผ่าตัดไส้ติ่งในระหว่างปีพุทธศักราชที่ 2546 ถึง 2559 เพื่อนำข้อมูลมาประเมินลักษณะทางพยาธิวิทยาและปัจจัยเสี่ยงที่นำไปสู่ความผิดปกติของไส้ติ่ง*

ผลการศึกษา: *ผู้ป่วยมะเร็งรังไข่ในการศึกษาครั้งนี้มีจำนวน 340 ราย พบว่า 322 รายเป็นมะเร็งรังไข่เยื่อบุผิวชนิดปฐมภูมิคิดเป็นร้อยละ 94.7 และร้อยละ 60.6 อยู่ในระยะแรก มิวซินัสคาร์ซิโนมาเป็นมะเร็งที่พบบ่อยที่สุดถึงร้อยละ 40 มะเร็งที่ไส้ติ่งพบในผู้ป่วยทั้งหมด 53 รายคิดเป็นร้อยละ 15.6 ของผู้ป่วยทั้งหมด โดยมีอยู่ 42 รายหรือร้อยละ 12.4 เกิดจากการแพร่กระจายมาจากมะเร็งรังไข่ และผู้ป่วยอีก 2 รายมีการแพร่กระจายมาจากกระเพาะอาหารและเต้านม ส่วนมะเร็งปฐมภูมิของไส้ติ่งพบได้ 9 ราย ในจำนวนเก้ารายนี้ มีอยู่ 3 สามรายที่พบว่าเป็นมะเร็งปฐมภูมิถึงสองชนิดคือมะเร็งไส้ติ่งเองและมะเร็งเยื่อบุผิวรังไข่ร่วมด้วย ปัจจัยที่มีผลต่อลักษณะทางพยาธิวิทยาของไส้ติ่งจากการวิเคราะห์ถดถอยโลจิสติกได้แก่ ลักษณะทางกายภาพของไส้ติ่งที่ผิดปกติขณะผ่าตัด (odds ratio 27.6, 95% confident interval 7.1–107.3, $p < 0.001$) มะเร็งรังไข่ที่พบมีการลุกลามออกนอกรังไข่ (odds ratio 114.6, 95% confident interval 14.6-99.4, $p < 0.001$) และมะเร็งรังไข่ชนิดทุติยภูมิ (odds ratio 86.7, 95% confident interval 8.5-887.7, $p < 0.001$)*

สรุป: *ขณะทำการผ่าตัดรักษามะเร็งของรังไข่สามารถพบมะเร็งที่ไส้ติ่งร่วมด้วยได้ ทางคณะผู้วิจัยจึงแนะนำให้มีการผนวกการตัดไส้ติ่งเป็นส่วนหนึ่งของขั้นตอนการผ่าตัดรักษามะเร็งรังไข่ด้วยในผู้ป่วยที่ไส้ติ่งดูผิดปกติขณะผ่าตัดช่องท้อง ในมะเร็งรังไข่ระยะลุกลาม และในมะเร็งรังไข่ชนิดทุติยภูมิ*

คำสำคัญ: *ตัดไส้ติ่ง, ไส้ติ่ง, มะเร็งรังไข่, พยาธิวิทยา*

Introduction

Recommendations for routine appendectomy in the management of ovarian cancer remain unclear. International Federation of Gynecology and Obstetrics (FIGO) Committee[1] and National Comprehensive Cancer Network[2] guidelines recommend routine appendectomy for mucinous ovarian cancer to differentiate between primary ovarian origin and secondary metastasis from the appendix, and also as part of cytoreductive surgery for optimal tumor debulking. Some studies have reported a significant rate of upstaging in early-stage disease owing to isolated occult appendiceal metastasis and a high rate of appendiceal metastasis in the advanced stage[3-5]. However, other studies have not recommended routine appendectomy because of a low rate of appendiceal involvement in early-stage disease[6, 7]. This study aimed to evaluate the prevalence of appendiceal pathology in patients undergoing surgical staging and selected appendectomy to treat ovarian cancer and identify factors that increase its risk.

Materials and Methods

This retrospective study was conducted in Songklanagarind Hospital, a tertiary referral center in southern Thailand. This study was approved by the Human Ethics Committee of the Faculty of Medicine, Prince of Songkhla University. The requirement for informed consent was waived given the anonymity of the routine data. We reviewed the medical records of patients diagnosed with ovarian cancer classified according to the FIGO staging system[2, 8, 9] between 2003 and 2016. The inclusion criteria were: 1) patients with primary epithelial and secondary ovarian cancer, 2) who had undergone primary or interval cytoreductive surgery and appendectomy depending on the intraoperative decision of the surgeon. The histological types of primary epithelial and secondary ovarian cancer were classified according to the World Health Organization classification[2, 8]. All pathologic slides were reviewed by the pathologist in our study. The exclusion criteria were 1) patients who had a sex cord-stromal tumor or germ cell tumor, 2) who underwent prior appendectomy, 3) who did not have an appendix pathological report and 4) incomplete data.

The sample size was calculated based on a 37% appendiceal metastasis rate in ovarian carcinoma[3], indicating that a total of 335 patients would be necessary for the analysis. Appendiceal pathology was defined according to the World Health Organization classification of tumors of the appendix[10]. The definition of coexisting ovarian and appendiceal tumors or synchronous primary tumors was established according to morphology, pattern of tumor spreading, immunohistochemistry, and genetic analysis[11-13]. A grossly abnormal appendix was considered to involve mucocele, thickening of the appendiceal wall, adhesions, tumor implants, nodules, mass, swelling, hyperemia, and distension, which were examined through visual inspection and palpation. Statistical analysis was performed using Statistical Package for the Social Science version 17 package program (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as median and range. Categorical variables were presented as counts and percentages. Patient characteristics were analyzed by student t-test for continuous variables and Chi-squared test for categorical variables. Univariate and multivariate analyses were performed. P values less than 0.05 were considered statistically significant.

Results

Patient and clinicopathological characteristics

Among the 1716 ovarian cancer patients at the time period, 340 patients were included and their clinicopathological characteristics are shown in Table 1. The most common histological type was mucinous tumor. Most patients had been diagnosed with primary epithelial ovarian cancer and 18 (5.3%) had been diagnosed with secondary ovarian cancer. Of 322 patients with primary epithelial ovarian cancer, most (43.5%) had stage I disease. Of 340 patients, 332 (97.7%) had undergone radical surgery, and eight (2.3%) patients with early-stage disease had undergone conservative surgery.

Table 1. Clinicopathological characteristic of the patients.

Characteristics (n = 340)	n (%)
Age (years), median (range)	50 (12–85)
FIGO stage	
Stage I-II	206 (60.6)
Stage III-IV	116 (34.1)
Metastases secondary to:	
Colorectal cancer	6 (1.8)
Appendix	6 (1.8)
Stomach	4 (1.1)
Breast	1 (0.3)
Thyroid	1 (0.3)
Histology	
Mucinous	136 (40.0)
Serous	76 (22.4)
Endometrioid	46 (13.5)
Clear cell	42 (12.4)
Adenocarcinoma	28 (8.2)
Mixed type	12 (3.5)
Ascites	
Mucin	27 (8.0)
Non-mucin	183 (53.8)
Cytology Positive	65 (19.1)
Tumor diameter (cm), median (range)	15 (2–60)
Tumor side: Bilateral	80 (23.5)
Peritoneal seeding	65 (19.1)
Presence of extraovarian tumor	178 (52.4)
Gross appearance of appendix Abnormal	29 (8.5)
Diameter of appendix (cm), median (range)	0.6 (0.5–6)
Length of appendix (cm), median (range)	5.0 (0.5–9)
Ovarian tumor	
Intact	190 (55.9)
Incidental rupture during operation	84 (24.7)
Previous rupture	59 (17.4)

Prevalence of appendiceal pathology in ovarian cancer

Of 340 patients, 53 (15.6%) had appendiceal pathology findings, including six (1.8%) with primary appendiceal cancer, three (0.9%) with coexisting or synchronous ovarian and appendiceal tumors, 42 (12.4%) with secondary appendiceal cancers that had metastasized from the ovary, and one with secondary appendiceal metastasis from the stomach and one from the breast. The clinical characteristics of the nine patients with primary appendiceal cancer and coexisting or synchronous appendiceal and ovarian tumors are shown in Table 2. Of six patients with primary appendiceal cancer, the gross appearance of the appendix was normal in two patients. Of three patients with synchronous appendiceal and ovarian tumors, one patient had a normal appendix.

Of 340 patients, 29 (8.5%) had a grossly

abnormal appendix, of whom 23 (79.3%) had abnormal histology findings. Of 311 patients with a healthy appearing appendix, 30 (9.6%) had appendiceal pathology.

Of 136 patients with ovarian cancer and a mucinous cell subtype, 11 (8.1%) had appendiceal pathology, which comprised primary mucinous appendiceal cystadenocarcinoma with metastasis to the ovary in five patients and secondary metastasis from ovarian cancer in six patients.

Table 2. Clinicopathological characteristics of patients with primary appendiceal tumors and synchronous ovarian and appendiceal tumors.

Patient	Age (years)	Ovary histology	Ovarian tumor status	Largest size of ovarian tumor (cm)	Ascites	Gross appearance of appendix intraoperatively	Tumor biochemical markers	Appendix histology
1	68	Mixed endometrioid and clear cell	Previous rupture	20	Straw color ascites 500 ml	Swelling	Not performed	Well-differentiated neuroendocrine tumor (carcinoid)
2	72	Serous cystadenocarcinoma	No rupture	10	None	Normal	Not performed	Mucinous cystadenoma
3	60	Clear cell	Accidental rupture	20	Straw color ascites 2400 ml	Mucocele	Not performed	Low grade mucinous cystadenocarcinoma
4	52	Metastasis from appendix	Previous rupture	25	Pseudomyxoma peritonei	Swelling	CK20 positive CK7 negative	Primary mucinous cystadenocarcinoma
5	77	Metastasis from appendix	Previous rupture	15	Pseudomyxoma peritonei	Mucocele	CK20 positive CK7 negative	Primary mucinous cystadenocarcinoma
6	50	Metastasis from appendix	Previous rupture	30	Pseudomyxoma peritonei	Mucocele	CK20 positive CK7 negative	Primary mucinous cystadenocarcinoma
7	68	Metastasis from appendix	Previous rupture	15	Pseudomyxoma peritonei	Normal	CK20 positive CK7 negative	Primary mucinous cystadenocarcinoma
8	34	Metastasis from appendix	Previous rupture	20	Serosanguinous ascites 200 ml	Phlegmon	CK20 positive CK7 negative	Primary adenocarcinoma
9	73	Metastasis from appendix	Previous rupture	15	Pseudomyxoma peritonei	Normal	CK20 positive CK7 negative	Primary mucinous cystadenocarcinoma

CK: cytokeratin

Prevalence of appendiceal pathology in primary epithelial ovarian cancer

Of 322 patients with primary epithelial and secondary ovarian cancer who had undergone primary or interval cytoreductive surgery and appendectomy depending on the intraoperative decision of the surgeon, 45 patients had appendiceal pathology, of whom 42 (13.0%) patients had secondary appendiceal metastasis from ovarian cancer, one had a carcinoid tumor, one had a primary appendiceal mucinous cystadenoma, and one had a primary appendiceal low grade mucinous cystadenocarcinoma.

Of 206 patients with early stage (I-II) epithelial ovarian cancer, one patient had a coexisting carcinoid appendiceal tumor. The rate of appendiceal metastasis from primary epithelial ovarian cancer was 36.2% (42 of 116 patients) in advanced-stage disease (III-IV) and none in early-stage disease.

Factors associated with appendiceal pathology

Of 340 patients, 53 had appendiceal pathology and 287 had a normal appendix histology. Potential factors associated with appendiceal pathology are shown in Table 3. In the multiple logistic regression analysis (Table 4) after being adjusted by the significant variables ($p<0.05$) from univariate analysis, appendiceal pathology was found to be significantly associated with the presence of a grossly abnormal appendix, advanced-stage disease of primary epithelial ovarian cancer, and secondary ovarian cancer.

Table 3. Univariate analysis of factors associated with appendiceal pathology.

Variable	Appendiceal pathology (n=53) n (%)	No appendiceal pathology (n=287) n (%)	OR (95% CI)	p value
Age (years)				
≤ 45	13 (11.8)	97 (88.2)	1	0.2
> 45	40 (17.4)	190 (82.6)	1.6 (0.8–3.1)	
FIGO Stage				
Stage I-II	1 (0.5)	205 (99.5)	1	<0.001
Stage III-IV	44 (37.9)	72 (62.1)	125.3 (16.9–925.8)	
Metastasis	8 (44.4)	10 (55.6)	164.0 (18.6–1441.5)	
Histology				
Mucinous	11(8.1)	125 (91.9)	1	<0.001
Serous	24 (31.6)	52 (68.4)	5.2 (2.4–11.4)	
Others	18 (14.1)	110 (85.9)	1.9 (0.8–4.1)	
Ascites				
Absent or non-mucin	47 (15.0)	266 (85.0)	1	0.3
Mucin	6 (22.2)	21 (77.8)	1.6 (0.6–4.2)	
Cytology				
Negative	20 (9.5)	191(90.5)	1	<0.001
Positive	17 (26.2)	48 (73.8)	3.4 (1.6–6.9)	
No data	16 (25.0)	48 (75.0)	-	
Tumor side				<0.001
Left side	12 (10.0)	108 (90.0)	1	
Right side	12 (8.6)	128 (91.4)	0.8 (0.3–1.9)	
Bilateral	29 (36.3)	51 (63.7)	5.1 (2.4–10.8)	
Tumor diameter (cm)				
≤10	18 (19.6)	74 (80.4)	1	0.2
>10	32 (14.2)	194 (85.8)	0.7 (0.3–1.2)	
No data	3 (13.6)	19 (86.4)	-	
Peritoneal seeding				
No seeding	25 (9.1)	250 (90.9)	1	<0.001
Seeding	28 (43.1)	37 (56.9)	7.6 (3.9–14.4)	
Extraovarian tumor				
No	7 (4.3)	155 (95.7)	1	<0.001
Yes	46 (25.8)	132 (74.2)	7.7 (3.4–17.6)	
Gross of appendix				
Normal	30 (9.6)	281 (90.4)	1	<0.001
Abnormal	23 (79.3)	6 (20.7)	35.9 (13.5–95.1)	
Diameter of appendix (cm)				
< 1	32 (12.3)	229 (87.7)	1	<0.001
≥ 1	19 (45.2)	23 (54.8)	5.9 (2.9–12.0)	
No data	2 (5.4)	35 (94.6)	-	
Ovarian tumor				
Intact or incidental rupture	39 (14.2)	235 (85.8)	1	0.1
Previous rupture	13 (22.0)	46 (78.0)	1.7 (0.8–3.4)	
No data	1 (14.3)	6 (85.7)	-	

CI: confidence interval, OR: odds ratio

Table 4. Multiple logistic regression analysis of factors associated with appendiceal pathology.

Variables	Adjusted OR (95% CI)	p value
FIGO stage		
Stage I-II	1	<0.001
Stage III-IV	114.6 (14.6–901.4)	
Metastasis	86.7 (8.5–887.7)	
Gross appearance of appendix		
Normal	1	<0.001
Abnormal	27.6 (7.1–107.3)	

Adjusted for age, histology, cytology, status of ovarian capsule, peritoneal seeding, and extraovarian tumor.
CI: confidence interval, OR: odds ratio

Prevalence of appendectomy associated complications

One patient had a suspected bowel perforation two weeks after an operation for stage IIIC mucinous cystadenocarcinoma. The second operation revealed an acute suppurative inflammation.

Discussion

This retrospective study evaluated the prevalence of appendiceal pathology in ovarian cancer patients undergoing primary or interval cytoreductive surgery and appendectomy depending on the intraoperative decision of the surgeon and also determined factors that increased its risk. In this study, the overall prevalence of appendiceal pathology in ovarian cancer was 15.6%, comprising 12.4% (42 of 340) of patients with secondary appendiceal metastasis from ovarian cancer and 2.6% (9 of 340) of patients with primary appendiceal cancer and coexisting ovarian and appendiceal tumors. The actual rate of primary appendiceal cancer and coexisting appendiceal and ovarian tumors during surgical treatment for ovarian cancer is unknown. However, Timofeev et al[14] reported that the prevalence of primary appendiceal cancers diagnosed during surgical exploration for a pelvic mass was 10.5% (20 of 191 study patients), and Wong et al[15] reported the prevalence of primary appendiceal cancer to be 4.2% in 9 of 213 patients in their study.

Regarding the gross appearance of the appendix, the rate of appendiceal pathology in a grossly abnormal appendix was 79.3%, which was relatively high compared to the findings of Timofeev et al[14]. This result supports our general practice, which advocates appendectomy in cases of an abnormal gross appearance of the appendix.

Regarding the mucinous histological subtype of ovarian tumors, appendectomy is recommended to distinguish the primary appendiceal origin. In this study, the rate of appendiceal pathology from a total of 136 patients with ovarian cancer of a mucinous cell subtype was 8.1%. These findings are similar to the results of a meta-analysis by Cheng et al[16], which included a total of 353 patients with mucinous ovarian cancer who underwent appendectomy; they estimated the rate of appendiceal pathology to be 6.3% and as high as 59% for patients with an abnormal gross appearance of the appendix. Feigenberg et al[17] studied a total of 77 patients with mucinous adenocarcinoma and mucinous borderline tumor; among them, 11 patients (14%) were diagnosed with primary appendiceal carcinoma with metastasis to the ovary and none had secondary appendiceal metastasis from the ovary. Of those 11 patients, 72.7% (8/11) had a grossly abnormal appendix. They concluded that there was insufficient evidence to support routine appendectomy in patients with a normal gross appearance of the appendix[16, 17].

The prevalence of appendiceal metastasis in primary epithelial ovarian cancer was found to be 13.0% in this study. Most appendiceal metastasis (36.2%, [42/116]) occurred in advanced-stage disease, whereas none occurred in the early stage, which was comparable to findings reported in several

other studies[3, 5-7, 14, 18]. Most studies have reported a high rate of appendiceal involvement in patients with a serous cell subtype and advanced-stage disease[3, 5, 14, 18]. A high prevalence of appendiceal metastasis in advanced-stage disease (42.2-71.8%)[3, 5, 14, 18] has also been reported in contrast to a very low rate in early-stage disease[3, 5-7, 14, 18].

Considering the outcomes of microscopic appendiceal metastasis, 8.4% (26/311) of patients whose appendix appeared to be normal had occult metastasis from the ovary. Of 26 patients, 25 had stage III-IV disease, and all these patients had other evidence of advanced-stage disease. Therefore, additional appendectomy did not alter the final stage but could have been beneficial for optimal cytoreductive surgery.

In this study, factors significantly associated with appendiceal pathology included advanced-stage disease of primary epithelial ovarian cancer, secondary ovarian cancer, and a grossly abnormal appearance of the appendix. Previous studies have reported a higher rate of appendiceal metastasis in patients with advanced-stage disease[3, 5] and a grossly abnormal appendix[14]. In contrast, Kokanali et al[18] reported tumor grade, the presence of ascites, the right side of the tumor, and large tumor size (>10 cm) as factors that significantly increased the risk of appendiceal metastasis, which were not found to be significant factors in our study. Performing a comprehensive exploration intraoperatively at the time of surgical treatment for ovarian cancer is important as is a careful evaluation of the appendix and removal of all suspected abnormal diseased tissue. Most studies[3, 5] recommend routine appendectomy; however, an appendectomy is not without risk, and complications such as intraabdominal abscess, intestinal obstruction, bowel perforation, and stump leakage can occur.

Al-Temimi et al[19] reported that incidental appendectomy increased the risk of morbidity in patients undergoing elective surgery (odds ratio (OR) 1.31, 95% confidence interval (CI) 1.03-1.68), and that it was also associated with an increased risk of postoperative wound complications (OR 1.46, 95% CI 1.05-2.03). In our study, one patient was diagnosed with appendiceal site perforation two weeks after primary surgery, and the rate of appendectomy associated complications was 0.3% (1/340).

In spite of the significant number of appendiceal pathologies in ovarian cancer of our study, this is limited by a retrospective in design and might have some missing data. In addition, the details of clinical treatment and data varied across the study. Even the treatments followed the guideline of the institute but were done by many surgeons. The decision of whether to remove the appendix intraoperatively remains individual and there is bias. The differing incidence of a more proportion of mucinous cancer than previous studies, as well as the different distribution of ovarian cancer subtypes, should be further explored, as these may provide insight into the mechanisms of ovarian carcinogenesis.

Conclusion

In conclusion, the study has shown that there is a potential for appendiceal pathology in patients who are presented with a grossly abnormal appendix, secondary ovarian cancer, or advanced-stage (III-IV) primary epithelial ovarian cancer. The distribution of appendiceal histology and the origin of the cancer prompts surgeons to consider appendectomy as part of surgical staging in relation to ovarian cancer clinical practice.

Potential conflicts of interest

The authors declare no conflicts of interest.

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