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Survival impact of capsule status in stage I ovarian mucinous carcinoma—A mulicentric retrospective study

Hiroaki Kajiyama[a,*], Shiro Suzuki[a], Nobuhisa Yoshikawa[a], Michiyasu Kawai[b], Tetsuro Nagasaka[c], Fumitaka Kikkawa[a]

[a] From Department of Obstetrics and Gynecology, Graduate School of Medicine, Nagoya University, Japan
[b] Department of Obstetrics and Gynecology, Toyohashi Municipal Hospital, Japan
[c] Division of Medical Laboratory Sciences, School of Health Science, Nagoya University, Japan

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ABSTRACT

Background: The influence of capsule rupture on patients' oncologic outcome has been controversial in early-stage ovarian carcinoma. The aim of this study was to investigate the significance of the capsule status in early-stage patients with mucinous epithelial ovarian carcinoma (mEOC).
Patients and methods: During the period of 1990–2015, 351 patients with stage I-IV mEOC were identified in the multicentric database. Of these, a total of 194 mEOC patients with a stage I tumor were in the study.
Results: The median follow-up of the surviving patients was 67.6 (2.0–248.1) months. The FIGO stage distribution was IA in 85 (43.8%), IB in 2 (1.0%), IC1 in 58 (29.9%), IC2 in 18 (9.3%), and IC3 in 31 (16.0%). The 5-year overall survival (OS) rates in patients with stage IA-B, IC1, and IC2-3 tumors were 95.8, 82.5, and 82.9%, respectively {IA-B vs. IC1: $P = 0.0031$, IA vs. IC2-3: $P = 0.0042$}. Similarly, the 5-year recurrence-free survival rates in patients with stage IA-B, IC1, and IC2-3 tumors were 93.5, 73.0, and 79.2%, respectively (Log-rank: $P = 0.0034$). Among all patients, 104 received adjuvant chemotherapy and 90 did not. There was no significant difference in each substage group between the non-chemotherapy and chemotherapy groups in the 5-year overall survival rate {chemotherapy (yes vs. no): 87.0 vs. 90.3%: $P = 0.5389$}. Multivariate analysis demonstrated that the capsule status was a significant prognostic factor for OS {IA-B (referent) vs. IC1: HR (95% CI): 3.527 (1.125–12.568), $P = 0.0300$)}.
Conclusion: mEOC patients staged greater than IC1 show a marked risk of mortality even after postoperative chemotherapy.

Introduction

Epithelial ovarian carcinoma (EOC) is the leading cause of death from gynecological malignancy [1]. Based on morphological criteria, there are four major histological types of EOC: serous, mucinous, endometrioid, and clear-cell histologies. Despite the fact that all patients with EOC have been similarly treated, clinical and biological behaviors differ in each histological subtype [2]. Mucinous epithelial ovarian carcinoma (mEOC) is a comparatively uncommon malignancy, accounting for approximately less than 10% of all ovarian carcinomas [3]. Generally speaking, mEOC displays a clinical behavior different from that of other histological types. mEOC is the most frequent pathological type in young women with EOC [4]. Patients with advanced mEOC a show lower sensitivity to platinum–based chemotherapy and a poorer oncologic outcome [5,6].

On the other hand, a prior study reported that, in patients with EOC aged ≤40 years, 30% had stage I disease and 8% had a mucinous type [7]. Reflecting the relatively slow-growing characteristics of this tumor at earlier stages, the prognosis of patients with early-stage mEOC has been reported to be favorable [3]. In addition, at the initial diagnosis, mEOC frequently presents as a huge abdominal tumor. Thus, a number of patients with this tumor are assigned to stage IC since the capsule either pre- or intraoperatively ruptures regardless of capsule surface involvement or positive cytology of ascites. The impact of capsule rupture on clinical outcomes in early-stage EOC patients was controversial among earlier studies [8–10]. Thus, according to the FIGO staging system 2014, stage IC is subdivided into intraoperative rupture (IC1), pre-operative

Abbreviations: mEOC, mucinous epithelial ovarian carcinoma; OS, overall survival; RFS, recurrence-free survival.

* Corresponding author at: Truma-cho 65, Showa-ku, Nagoya, 466-8550, Japan.
E-mail address: kajiyama@med.nagoya-u.ac.jp (H. Kajiyama).

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rupture (IC2), and malignant ascites or peritoneal washings (IC3) [11]. Presumably, the existence of positive malignant cells in ascites/washing suggests the presence of microscopic capsule rupture. Thus, stage I substage was paraphrased as the capsule status. Based on each histologic type, intraperitoneal behaviors of tumors and neighboring environments were different, including the character of readily adhering to surrounding tissue, presenting tumor size, and highly metastatic potential. In clinical practice, mEOC patients staged IC1 or IC2/3 are less frequent than those with stage IA tumors.

In the present study, we evaluated the oncologic outcomes of patients with ovary-confined mEOC to determine the impact of intra- and preoperative capsule rupture. We conducted a retrospective study analyzing 194 patients who were accumulated in a total of 14 Japanese university / general hospitals under a central pathological review system.

Patients and methods

Patient enrollment

Patients with malignant ovarian tumors were registered and accumulated by the Tokai Ovarian Tumor Study Group (TOTSG), consisting of Nagoya University Hospital and 13 affiliative institutions. All histological slides were reviewed by two expert pathologists with no knowledge of the patients' clinical data under a central pathological review system. Between 1990 and 2015, 351 patients with mEOC were identified in this registry system. Eligible cases included: (1) Patients who received initial surgery and periodic follow-up at the aforementioned institutions; and (2) patients for whom there was sufficient information about the primary surgery, first-line chemotherapy, and date of recurrence or death. Patients were excluded from this study if they had insufficient clinical data or a history of other malignancies, or were lost to follow-up immediately after surgery. Of these, 241 patients with transient mEOC/stage I (Tumors limited to the ovaries) were extracted. Furthermore, 47 patients were excluded from this study due to: 1) missing information on the substage (N = 4), 2) missing information on the final oncologic outcome (N = 7), and 3) missing information on chemotherapy (N = 36). In the present study, 194 patients with mEOC/stage I tumors were finally enrolled (Fig. 1). As the histological types, we adopted the World Health Organization (WHO) classification criteria. The clinical stage was assigned according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [11,12]. Namely, according to capsule status, stage I substage was defined as follows: IA: Tumor limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings, IC1: Tumor limited to 1 or both ovaries with intraoperative surgical spill, negative malignant cells in ascites or peritoneal washings, IC2: Tumor limited to 1 or both ovaries with preoperative capsule ruptured or tumor on ovarian or fallopian tube surface, IC3: Tumor limited to 1 or both ovaries with positive malignant cells in the ascites or peritoneal washings.

In patients with mEOC, we excluded those with metastatic secondary ovarian tumors based on several reference criteria, as follows [13]: (1) absence of segmental necrosis of tumoral glands, which is characteristic of metastatic colorectal carcinoma, (2) absence of apparent signet ring cells, (3) absence of any history of gastrointestinal carcinoma, and (4) in the majority of patients, immunohistochemical analysis, including cytokeratins 7 and 20 (CK7/20) and CDX-2 (caudal-related homeobox gene type 2), was conducted for pathological diagnosis. This study was approved by the ethics committee of Nagoya University.

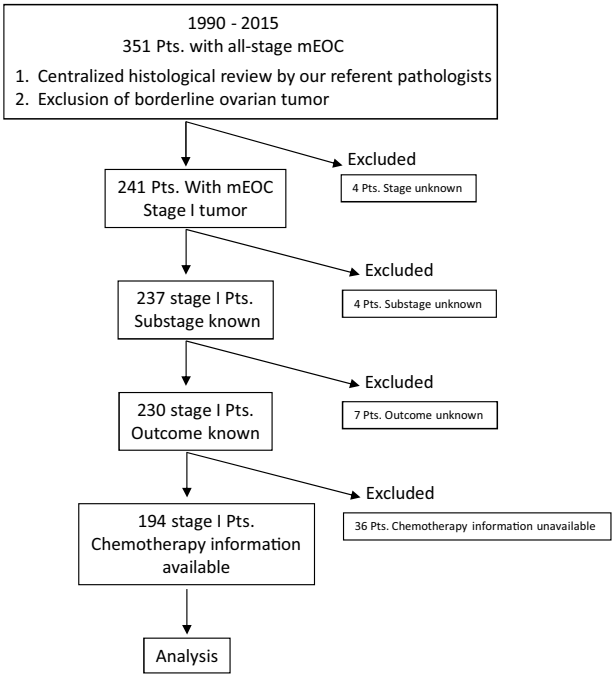

Fig. 1. Patient flowchart.

Treatment

Primary laparotomy was conducted in all patients for assessment of the abdominal contents. In principle, standard primary surgical treatment consisted of hysterectomy, bilateral salpingo-oophorectomy, and complete staging. Forty-one patients underwent conservative surgery because they hoped to preserve fertility or were young. Complete staging surgery was defined as peritoneal staging and lymph node evaluation. Peritoneal staging included peritoneal exploration, cytology, biopsy, and/or omentectomy or omental biopsy. Lymph node evaluation involved one of the following: 1) lymph node dissection, 2) lymph node sampling, or 3) palpation and removal of enlarged lymph nodes. In all, chemotherapy was in principle recommended for all patients; however, in 90 women, this was not done. If patients were at an advanced stage, or showed severe perioperative complications and/or comorbidity, chemotherapy was not performed at each surgeon's discretion. Policies on chemotherapeutic agents varied according to time; however, we basically have used the same selection criteria for first-line regimens as TOTSG. Details of the chemotherapy regimen during each period were described previously [14].

Follow-up and analysis

At the end of treatment, all patients underwent a strict follow-up, consisting of clinical checkups such as a pelvic examination, ultrasonographic scan, CA125 evaluation, and periodic radiologic imaging. Radiologic recurrence was defined as tumor recurrence based on computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and/or ultrasound, and clinical recurrence was defined as the development of ascites, elevated CA125, or a clinically palpable mass according to the Gynecologic Cancer InterGroup (GCIG) criteria in principle [15]. The overall survival (OS) was defined as the time between the date of surgery and the last date of follow-up or death from any cause. Recurrence-free survival (RFS) was defined as the time interval between that of surgery and the date of recurrence or death or the last follow-up. Survival curves were based on the Kaplan–Meier method. The survival curves were compared employing the Log-

rank test. Multivariable analysis was performed using the Cox proportional hazards model to evaluate independent factors affecting survival.

A *P*-value of <0.05 was considered significant.

Results

Patients' characteristics

The characteristics of enrolled patients are presented in Table 1. The median (range) age was 50 (12–91 years) years. The median follow-up periods for surviving patients was 67.6 (2.0–248.1) months. The FIGO stage distribution was IA in 85 (43.8%), IB in 2 (1.0%), IC1 in 58 (29.9%), IC2 in 18 (9.3%), and IC3 in 31 (16.0%). The patient distribution on stratification by age was ≤50: 100 (51.5%), and >50: 94 (48.5%). Sixty-nine patients (35.6%) received taxane plus platinum, and 35 patients (18.0%) received conventional platinum-based chemotherapy. In half of the patients (N = 95: 49.0%), the preoperative CA125 value was elevated to over 35 U/mL.

Oncologic outcome

On following up a total of 194 patients, 36 patients (18.6%) developed recurrence. In addition, 27 patients (13.9%) died of recurrence.

Fig. 2 shows OS curves on stratification by the substage reflecting the capsule status. The 5-year overall survival rates were as follows: 95.8% (IA), 82.5% (IC1), and 82.9% (IC2-IC3), (*P* = 0.0077: comparison of the three groups). There was a significant difference in OS between patients with IA and those with IC1 or IC2/3 (IA vs. IC1: P = 0.0031, IA vs. IC2/3: P = 0.0042, respectively). Fig. 3 shows RFS curves on stratification by the substage reflecting the capsule status. The 5-year recurrence-free survival rates were as follows: 93.5 % (IA), 70.0 % (IC1), and 79.2 % (IA), 73.0% (IC1), and 79.2% (IC2-IC3), (*P* = 0.0034: comparison of the three groups). There was a significant difference in RFS between patients with IA and those with IC1 or IC2/3 (IA vs. IC1: P = 0.0018, IA vs. IC2/3: P = 0.0020, respectively). We finally examined whether adjuvant chemotherapy affects the clinical outcome. Among all patients, 104 patients received adjuvant chemotherapy and 90 patients did not. As shown in Fig. 4, we did not identify any significant differences in OS between the two cohorts {the 5-year OS rates: 87.0% (present) vs. 90.3% (absent): *P* = 0. 5389}.

To eliminate selection bias from a number of clinicopathologic factors as thoroughly as possible, we finally performed multivariate OS analyses. The age (≤50 vs. >50), FIGO stage {IA-B (referent) vs. IC1 vs. IC2/3)}, ascites volume (≤100 vs. >100 mL), ascites cytology type (Negative/False positive vs. Positive), ascites cytology type (Negative vs. False-positive / positive), preoperative CA125 value (≤35 vs. >35 U/mL), and chemotherapy {taxane plus ptitinum (referent) vs. platinum-based vs. none}, were entered into the uni- and multivariate OS analyses (Tables 2 and 3). In the univariate analysis, the substage, ascites volume, and preoperative

Table 1
Patients' characteristics.

	N	%
Total	194	
Age		
(Median range)	50 (12–91)	
≤50	100	51.5
>50	94	48.5
FIGO stage		
I		
IA	85	43.8
IB	2	1.0
IC1	58	29.9
IC2	18	9.3
IC3	31	16.0
Ascites volume		
≤100 mL	150	77.3
>100 mL	44	22.7
Ascites cytology		
Negative	148	76.3
False-positive	15	7.7
Positive	31	16.0
CA125 value		
≤35 U/mL	99	51.0
>35 U/mL	95	49.0
Chemotherapy		
Taxane plus platinum	69	35.6
Platinum-based	35	18.0
None	90	46.4

FIGO: International Federation of Gynecology and Obstetrics, IC substage was defined according to FIGO 2014 classification.

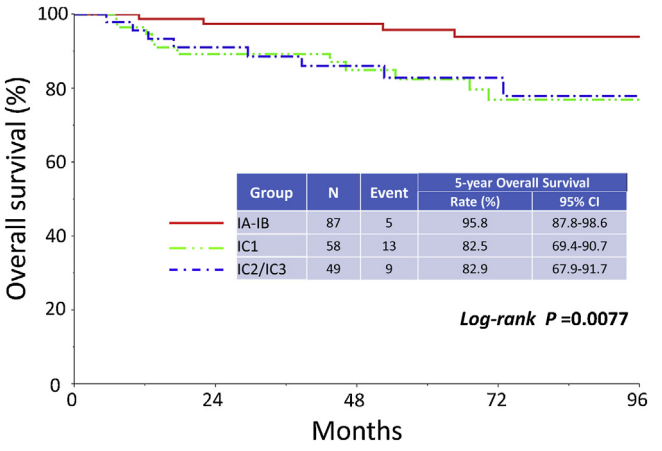

Fig. 2. Kaplan–Meier estimated overall survival of patients with stage I mucinous epithelial ovarian carcinoma (mEOC). Stage IA-B (solid line, N = 87), stage IC1 (intraoperative capsule rupture: two-dotted chain line, N = 58), and stage IC2/3 (preoperative capsule rupture/capsule involvement: dotted black line, N = 49). Three group comparison: Log-rank: P = 0.0077. There was significant difference in OS between patients with IA and those with IC1 or IC2/3 (P = 0.0031 and P = 0.0042, respectively).

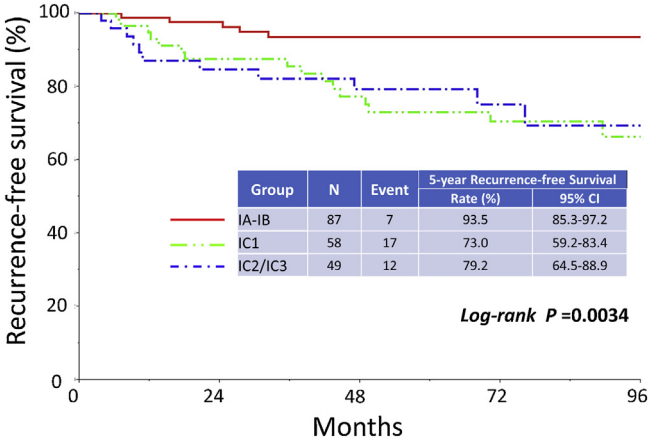

Fig. 3. Kaplan–Meier estimated recurrence-free survival of patients with stage I mucinous epithelial ovarian carcinoma (mEOC). Stage IA-B (solid line, N = 87), stage IC1 (intraoperative capsule rupture: two-dotted chain line, N = 58), and stage IC2/3 (preoperative capsule rupture/capsule involvement: dotted black line, N = 49). There was significant difference in RFS between patients with IA and those with IC1 or IC2/3 (P = 0.0018 and P = 0.0020, respectively).

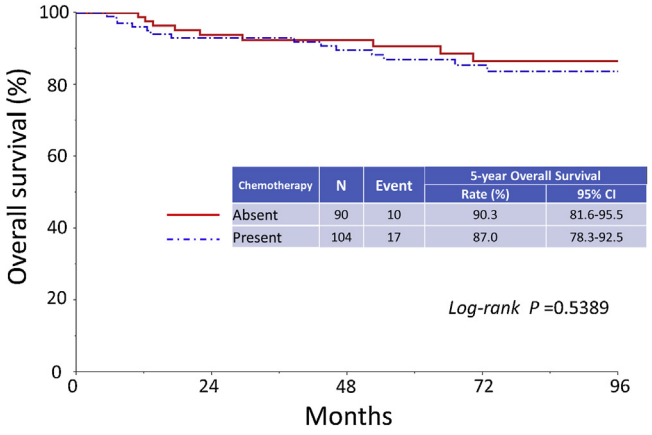

Fig. 4. Kaplan–Meier estimated overall survival of mEOC patients with or without adjuvant chemotherapy. Absent chemotherapy (solid line, N = 90), Present chemotherapy (one-dotted chain line, N = 104). There was no significant differences in OS between the two cohorts {the 5-year OS rates: 87.0% (present) vs. 90.3% (absent): Log-rank: *P* = 0. 5389}.

Table 2
Univariate analysis in Cox Hazard Model.

	Overall survival		
	HR	95 % CI	*P*
Age			
≤50	1		
>50	1.415	0.650–3.129	0.3792
FIGO stage			
IC1	1		
IA-B	0.240	0.076–0.637	0.0037
IC2-IC3	1.008	0.412–2.368	0.9848
Ascites volume			
≤100 mL	1		
>100 mL	2.637	1.180–5.711	0.0191
Ascites cytology			
Negative/False-positive	1		
Positive	0.924	0.270–2.420	0.8849
CA125 value			
≤35 U/mL	1		
>35 U/mL	3.025	1.335–7.730	0.0072
Chemotherapy			
Taxane plus platinum	1		
Platinum-based	1.463	0.525–4.025	0.4552
None	0.779	0.272–2.174	0.6297

FIGO: International Federation of Gynecology and Obstetrics, HR: hazard ratio, 95% CI: 95% confidence interval.

CA125 value were significant indicators of poorer OS. However, in multivariate analysis, only the substage retained its significance for OS {IA-B (referent) vs. IC1: HR (95% CI): 3.527 (1.125–12.568), P = 0.0300), IA-B (referent) vs. IC2/3: HR (95% CI): 3.839 (1.032–15.872), P = 0.0445)} (Tables 2 and 3).

We finally investigated the site of recurrence in all patients who developed it. Fig. 5 shows the distributions of recurrence per each substage's total cases. As a result, the rates of recurrence including the peritoneum were 57.1 (4/7), 64.1 (11/17), and 50.0 (6/12) in patients at stage IA, IC1, and IC2/3, respectively (P = 0.7294).

Discussion

In the clinical practice of treating early-stage EOC patients, rupture of the tumor capsule is divided into two major groups:

Table 3
Multivariate analysis in Cox Hazard Model.

	Overall survival		
	HR	95 % CI	*P*
Age			
≤50	1		
>50	1.092	0.454–2.630	0.8412
FIGO stage			
IA-B	1		
IC1	3.527	1.125–12.568	0.0300
IC2-IC3	3.839	1.032–15.872	0.0445
Ascites volume			
≤100 mL	1		
>100 mL	1.598	0.671–3.725	0.2834
Ascites cytology			
Negative/False-positive	–		
Positive	–	–	–
CA125 value			
≤35 U/mL	1		
>35 U/mL	1.860	0.730–5.285	0.1995
Chemotherapy			
Taxane plus platinum	1		
Platinum-based	1.480	0.506–4.308	0.4670
None	1.917	0.608–5.853	0.2586

FIGO: International Federation of Gynecology and Obstetrics, HR: hazard ratio, 95% CI: 95% confidence interval.

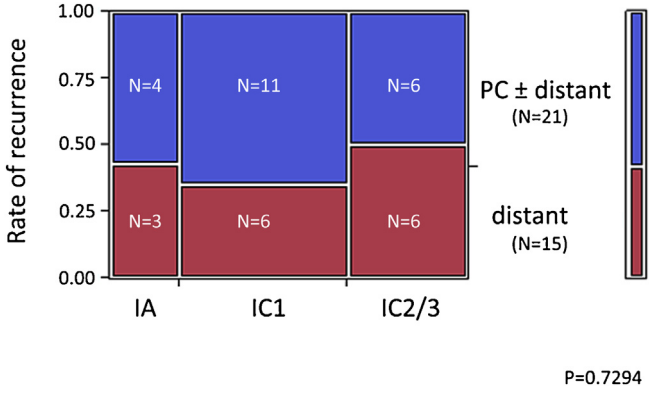

Fig. 5. The distributions of recurrence per each substage's total cases. The rates of recurrence including the peritoneum were 57.1 (4/7), 64.1 (11/17), and 50.0 (6/12), in patients at stage IA, IC1, and IC2/3, respectively (P = 0.7294).

spontaneous rupture before surgery and intraoperative rupture caused by manipulation. Basically, patients with preoperative capsule rupture or positive washing have a greater risk of recurrence and show poorer survival than those with encapsulated tumors. However, the influence of intraoperative capsule rupture on patients' oncologic outcome has been controversial. In an earlier large-scale study by Vergote et al., regardless of pre- or intraoperatively, capsule rupture led to a shorter disease-free survival [9]. On the other hand, according to a prior meta-analysis of 9 eligible studies including 2382 patients, intraoperative rupture may not decrease PFS when compared with no rupture in patients with early-stage EOC who underwent complete surgical staging operation and adjuvant platinum-based chemotherapy [16]. Essentially, EOCs are heterogeneous tumors, consisting of multiple histologic types. Therefore, due to this heterogeneity, the hallmarks of this disease are more complicated and various than expected. Therefore, it is desirable to examine whether the impact

of the capsule status on the long-term survival differs, based on each histological type.

Previous nationwide epidemiological surveys of gynecologic malignancy reported that mEOC accounted for approximately 10% of EOC [3,17]. Typical characteristics of primary mEOC are as follows: 1) relatively large, unilateral tumors, 2) with multiple smooth capsules, 3) less frequently associated with extra-ovarian metastasis, 4) more commonly associated with precursor borderline tumor, and 5) more frequently displaying confluent glandular or expansile patterns of invasion. [18]. Furthermore, mucinous tumors were generally less frequently associated with intraoperative rupture than no rupture [16].

Here, we examined 194 patients with stage I mEOC reassessed by centralized pathology review. We identified a significant difference in both overall and recurrence-free survival between those with stage IA and IC1, as well as between those with stage IA and IC2/3. These results suggest that intraoperative capsule rupture is a risk associated with a poorer oncologic outcome in patients with early-stage mEOC. According to our prior study, for patients with early-stage clear-cell carcinoma, intraoperative capsule rupture without negative ascites/washing was not a prognostic indicator threatening their oncologic outcome [19]. However, why does the difference occur? In general, both ovarian clear-cell and endometrioid carcinoma are regarded as two different clinical entities: endometriosis-associated carcinoma [20]. The capsule rupture of a clear-cell carcinoma is thought to be attributable to surgical dissection of the dense adhesion to the neighboring pelvic organs, more often associated with endometriosis rather than tumor invasion. On the other hand, mEOC is not associated with endometriosis. If such local adhesion between a tumor and surrounding tissues is present, it may be more frequently related to undiagnosable local tumor infiltration rather than endometriosis. This is a potential reason why mEOC patients with intraoperative capsule rupture showed a poorer prognosis in this study than expected.

Regardless of the presence or absence of surface invasion, capsule rupture may become a risk factor for recurrence because it has the possibility of generating widely-spreading “seeds of recurrence” in the peritoneal cavity. In clinical practice, we perform chemotherapy, expecting the complete elimination of these invisible “seeds” and prevention of future recurrence. Accordingly, in this study, we examined whether adjuvant chemotherapy affects the clinical outcome. Nevertheless, we did not identify any significant differences in overall survival between the chemotherapy-present and -absent cohorts {5-year OS rates: 87.0% (present) vs. 90.3% (absent): $P = 0.5389$}. Indeed, Shimada, et al. demonstrated that mEOC showed a weaker response to platinum-based chemotherapy (12.5%) than serous adenocarcinoma (67.7%) [21]. Moreover, a number of earlier studies indicated that patients with mEOC showed chemoresistant hallmarks to platinum-based chemotherapy [5,22,23]. Considering the biological characteristics of potential chemoresistance of this tumor, the postoperative chemotherapy did not have sufficient power to eliminate the occult clones. We should keep in mind that mEOC patients with both intrao- and preoperative capsule rupture / positive ascites may have a marked risk of recurrence and subsequent mortality.

The current study is inconclusive because of its retrospective nature and patient accumulation from multiple institutions over a long time. In addition, we were unable to evaluate explicit information about salvage chemotherapy and secondary cytoreductive surgery. Furthermore, mEOC occasionally presents as a huge, abdominal, cystic tumor, preoperatively considered as a benign or borderline mucinous tumor. In such a situation, surgeons tend to make a decision to aspirate the intratumoral fluid for surgical convenience. However, in this investigation, we could not examine the procedure of intraoperative content aspiration itself as an independent indicator. Thus, we do not think that the present results suggest the need to avoid intratumoral aspiration during surgery as long as it is done as carefully as possible to avoid spilling the fluid.

On the other hand, the strengths of our study included the centralized pathologic review by expert pathologists in gynecologic malignancy. Tumors initially identified as mEOC are frequently borderline malignancies, or metastatic carcinomas arising from the gastrointestinal tract [24]. It is very important to accurately discriminate primary mEOC from metastatic/secondary mucinous tumors that have metastasized to the ovaries from the gastrointestinal tract, through intraoperative surgical assessment and final pathologic diagnosis. In the current examination, we exerted a maximal effort to diagnose mEOC as precisely as possible. In addition, the central pathologic review enabled us to accomplish the unified evaluation of stromal invasion, which is generally considered difficult for mucinous tumors. Thus, reassessment of the pathological findings contributed to appropriate diagnosis and reduced intraobserver variability on determining the histological type. Additionally, the initial surgery and chemotherapy were carried out based on the same criteria and protocol in the identical study group (TSTOG group).

In conclusion, to our knowledge, this is one of the largest series on oncologic outcomes in mEOC patients focusing on the capsule status. Our data suggest that at surgery, we should try to remove the tumor as carefully as possible to avoid intraoperative rupture. Furthermore, in the current study, we showed that the performance of additional chemotherapy did not impact on any prognostic advantage. This result raises a very critical question whether chemotherapy in itself has a power to diminish invisible occult clone, leading to the improvement of survival time in this tumor. Although the present study includes many limitations, we could generate many hypotheses through our current work. We hope that the present results will be reassessed and verified by other researchers in a future trial, shedding new light on the optimal strategy to treat this tumor.

Conflict of interest statement

All authors declare that there are no conflicts of interest.

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References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.
[2] Salgado-Ceballos I, Rios J, Perez-Montiel D, Gallardo L, Barquet-Munoz S, Salcedo-Hernandez R, et al. Is lymphadenectomy necessary in mucinous ovarian cancer? A single institution experience. Int J Surg 2017;41:1–5.
[3] Chan JK, Teoh D, Hu JM, Shin JY, Osann K, Kapp DS. Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. Gynecol Oncol 2008;109:370–6.
[4] Yoshikawa N, Kajiyama H, Mizuno M, Shibata K, Kawai M, Nagasaka T, et al. Clinicopathologic features of epithelial ovarian carcinoma in younger vs. older patients: analysis in Japanese women. J Gynecol Oncol 2014;25:118–23.
[5] Hess V, A'Hern R, Nasiri N, King DM, Blake PR, Barton DP, et al. Mucinous epithelial ovarian cancer: a separate entity requiring specific treatment. J Clin Oncol 2004;22:1040–4.
[6] Kikkawa F, Nawa A, Kajiyama H, Shibata K, Ino K, Nomura S. Clinical characteristics and prognosis of mucinous tumors of the ovary. Gynecol Oncol 2006;103:171–5.
[7] Bozas G, Dimopoulos MA, Kastritis E, Efstathiou E, Koutsoukou V, Rodolakis A, et al. Young age is associated with favorable characteristics but is not an independent prognostic factor in patients with epithelial ovarian cancer: a single institution experience. Oncology 2006;70:265–72.

[8] Vergote I, De Brabanter J, Fyles A, Bertelsen K, Einhorn N, Sevelda P, et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet 2001;357:176–82.
[9] Suh DH, Park JY, Lee JY, Kim BG, Lim MC, Kim JW, et al. The clinical value of surgeons' efforts of preventing intraoperative tumor rupture in stage I clear cell carcinoma of the ovary: a Korean multicenter study. Gynecol Oncol 2015;137:412–7.
[10] Mizuno M, Kikkawa F, Shibata K, Kajiyama H, Ino K, Kawai M, et al. Long-term follow-up and prognostic factor analysis in clear cell adenocarcinoma of the ovary. J Surg Oncol 2006;94:138–43.
[11] Zeppernick F, Meinhold-Heerlein I. The new FIGO staging system for ovarian, fallopian tube, and primary peritoneal cancer. Arch Gynecol Obstet 2014;290:839–42.
[12] Chen VW, Ruiz B, Killeen JL, Cote TR, Wu XC, Correa CN. Pathology and classification of ovarian tumors. Cancer 2003;97:2631–42.
[13] Kajiyama H, Mizuno M, Shibata K, Kawai M, Nagasaka T, Kikkawa F. Extremely poor postrecurrence oncological outcome for patients with recurrent mucinous ovarian cancer. Int J Clin Oncol 2014;19:121–6.
[14] Suzuki S, Kajiyama H, Shibata K, Ino K, Nawa A, Sakakibara K, et al. Is there any association between retroperitoneal lymphadenectomy and survival benefit in ovarian clear cell carcinoma patients? Ann Oncol 2008;19:1284–7.
[15] Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer intergroup (GCIG). Int J Gynecol Cancer 2011;21:419–23.
[16] Kim HS, Ahn JH, Chung HH, Kim JW, Park NH, Song YS, et al. Impact of intraoperative rupture of the ovarian capsule on prognosis in patients with early-stage epithelial ovarian cancer: a meta-analysis. Eur J Surg Oncol 2013;39:279–89.
[17] Yamagami W, Aoki D. Annual report of the committee on gynecologic oncology, the Japan Society of Obstetrics and Gynecology. J Obstet Gynaecol Res 2015;41:1861–9.
[18] Ji H, Isacson C, Seidman JD, Kurman RJ, Ronnett BM. Cytokeratins 7 and 20, Dpc4, and MUC5AC in the distinction of metastatic mucinous carcinomas in the ovary from primary ovarian mucinous tumors: Dpc4 assists in identifying metastatic pancreatic carcinomas. Int J Gynecol Pathol 2002;21:391–400.
[19] Higashi M, Kajiyama H, Shibata K, Mizuno M, Mizuno K, Hosono S, et al. Survival impact of capsule rupture in stage I clear cell carcinoma of the ovary in comparison with other histological types. Gynecol Oncol 2011;123:474–8.
[20] Brilhante AV, Augusto KL, Portela MC, Sucupira LC, Oliveira LA, Pouchaim AJ, et al. Endometriosis and ovarian cancer: an integrative review (endometriosis and ovarian cancer). Asian Pac J Cancer Prev 2017;18:11–6.
[21] Shimada M, Kigawa J, Ohishi Y, Yasuda M, Suzuki M, Hiura M, et al. Clinicopathological characteristics of mucinous adenocarcinoma of the ovary. Gynecol Oncol 2009;113:331–4.
[22] Pectasides D, Fountzilas G, Aravantinos G, Kalofonos HP, Efstathiou E, Salamalekis E, et al. Advanced stage mucinous epithelial ovarian cancer: the Hellenic Cooperative Oncology Group experience. Gynecol Oncol 2005;97:436–41.
[23] Pisano C, Greggi S, Tambaro R, Losito S, Iodice F, Di Maio M, et al. Activity of chemotherapy in mucinous epithelial ovarian cancer: a retrospective study. Anticancer Res 2005;25:3501–5.
[24] Kelemen LE, Kobel M. Mucinous carcinomas of the ovary and colorectum: different organ, same dilemma. Lancet Oncol 2011;12:1071–80.