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Original Article

Impact of incomplete surgery and adjuvant chemotherapy for the intraoperative rupture of capsulated stage I epithelial ovarian cancer: a multi-institutional study with an in-depth subgroup analysis

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ABSTRACT

Objective: The aim of the present study was to examine the effects of incomplete surgery and adjuvant chemotherapy on the prognosis of patients with intraoperative rupture of capsulated stage I epithelial ovarian cancer (OvCa).
Methods: A regional retrospective study was conducted between 1986 and 2019. Among 4,730 patients with malignant ovarian tumors, 534 women with International Federation of Gynecology and Obstetrics stage IA and IC1 epithelial OvCa were eligible. Differences in survival outcomes were examined between patients with stage IA and IC1 tumors and the effects of uterine preservation, complete-staging lymphadenectomy, and adjuvant chemotherapy were investigated by an in-depth subgroup analysis. To analyze therapeutic effects, baseline imbalances were adjusted using propensity score (PS).
Results: The prognosis of patients with stage IC1 tumors was worse than those with stage IA. Surgical spill did not affect the site of recurrence. In the PS-adjusted subgroup analysis, uterine preservation (hazard ratio [HR]=1.669; 95% confidence interval [CI]=1.052–2.744), incomplete-staging lymphadenectomy (HR=1.689; 95% CI=1.211–2.355), and the omission of adjuvant chemotherapy (HR=3.729; 95% CI=2.090–6.653) significantly increased the HR of recurrence for patients with stage IC1 tumors compared to those with stage IA tumors. Adjuvant chemotherapy decreased the impact of rupture with uterine preservation (HR=0.159; 95% CI=0.230–1.168) or incomplete-staging lymphadenectomy (HR=0.987; 95% CI=0.638–1.527).
Conclusion: The present results suggest intraoperative rupture of capsulated stage I epithelial OvCa is associated with a poor prognosis. When chemotherapy is given for patients receiving incomplete surgery, there is no longer an increased risk of recurrence observed with the rupture.

Keywords: Adjuvant Chemotherapy; Fertility Effect; Lymph Node Excision; Ovarian Cancer; Rupture, Spontaneous

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No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Ovarian cancer (OvCa) is one of the leading causes of death in the gynecological field [1,2]. The majority of tumors are categorized as epithelial neoplasms and 50% of patients are diagnosed at an early stage [3]. Stage I patients, whose tumors are localized to the ovary, have a favorable survival outcome [4]. However, recurrence has been reported in approximately 10% of these patients [5], and tumors develop treatment resistance, representing refractory disease. Regarding treatment, complete tumor resection may be performed for the majority of stage I patients. Once the whole tumor is resected, primary guidelines allow full-staging surgery and adjuvant chemotherapy to be waived for some patients [6-8]. Therefore, gynecologists need to carefully select the best therapeutic strategy for each patient in consideration of minimal interventions that will not have a negative impact on prognosis.

Regarding sub-staging categories in stage I OvCa, few differences exist between stages IA and IC1, except for the intraoperative rupture of capsulated tumors of the ovary [9]. Previous studies reported the impact of capsule rupture in stage I epithelial OvCa [10-13]; the prognosis of patients with stage IC1 tumors was worse than those with stage IA tumors [10,11]. In contrast, a meta-analysis showed that survival did not significantly differ between stage IC1 patients who underwent complete-staging laparotomy and received adjuvant chemotherapy in stage IA/IB patients [12]. On the other hand, a recent large cohort study suggested that adjuvant chemotherapy had no beneficial effects on the cause-specific survival of patients with stage IC1 epithelial OvCa [13]. Therefore, the effects of complete-staging surgery and post-operative chemotherapy on the prognosis of patients with stage IC1 tumors remain unclear.

The surgical spill of capsulated stage I tumors occurs in up to 40% of patients with OvCa [14]. In addition, the rate of discordance in pathology for OvCa, e.g., a mucinous histology, between intraoperative frozen sections and the final diagnosis was found to be 34% [15]. These findings indicate that unpredictable tumor upstaging and upgrading occurs in some cases. Alternatively, uterine preservation or incomplete-staging lymphadenectomy is performed for young or elderly patients due to their hope for future pregnancy or a reduced performance status, respectively. Collectively, there is no clinical evidence to suggest that additional interventions for stage IC1 tumors are effective as a follow-up to initial surgery. In the present study, we investigated the prognostic impact of the intraoperative rupture of capsulated stage I epithelial OvCa on hazard ratio (HR) of recurrence. By using an in-depth subgroup analysis with propensity score (PS)-based statistical adjustments, we also investigated the impact of incomplete surgery, including uterine preservation and incomplete-staging lymphadenectomy, and post-operative chemotherapy on the prognosis of patients with stage IC1 and IA tumors.

MATERIALS AND METHODS

1. Study participants

We conducted a multi-institutional retrospective cohort study with data from the Tokai Ovarian Tumor Study Group composed of Nagoya University Hospital and affiliated institutions between January 1986 and September 2019. The present study was approved by the Ethics Committee of Nagoya University according to the principles of the Declaration of Helsinki (Approved No. 357).

We included women (1) who underwent surgery for stage I primary epithelial OvCa, in whom the tumor was confined to the ovary without pre-operative capsule rupture and/or a positive ascitic cytology; (2) with sufficient information on survival outcomes; and (3) with histopathological slides reviewed by an expert pathologist according to the criteria of the World Health Organization classification. The clinical stage was selected based on the staging system of the International Federation of Gynecology and Obstetrics (FIGO) [9]. We excluded patients without sufficient clinical data on survival outcomes or those lost to the follow-up immediately after primary surgery.

2. Surgery, chemotherapy, and follow-up

Primary surgery for stage I epithelial OvCa involved total hysterectomy and bilateral salpingo-oophorectomy with a full peritoneal evaluation, including peritoneal exploration, cytology, biopsy, and/or omentectomy, and staging lymphadenectomy. Full-staging lymphadenectomy was defined as resection of both the pelvic and para-aortic lymph nodes; pelvic node lymphadenectomy was conducted from the common, internal and external iliac, and obturator vessels to the femoral ring; and para-aortic lymphadenectomy covered the bifurcation of the aorta to the origin of renal vessels. Some patients underwent incomplete surgery, including uterine preservation and incomplete-staging lymphadenectomy, for clinical reasons including the sparing of fertility and a reduced performance status. Even in patients who underwent incomplete-staging lymphadenectomy, pelvic lymph node sampling or clinical lymph node evaluations based on the findings of radiological images or direct palpation during surgery were performed to investigate clinically-apparent lymph node metastasis. Details of adjuvant chemotherapy in each time period were previously reported [16]. All patients were regularly followed up until 10 years after the initial surgery with a pelvic examination, including ultrasonography, computed tomography, magnetic resonance imaging, or positron emission tomography, and the evaluation of tumor markers. A recurrent tumor was clinically defined as the development of ascites, a detectable mass, or elevated tumor markers mainly according to the criteria of the Gynecologic Cancer InterGroup [17]. The duration of recurrence-free survival was defined as the time from the date of initial surgery until that of the last follow-up or tumor recurrence.

3. Statistical analysis

We adjusted imbalances in the 2 groups with the PS method, in which scores were created by fitting a logistic regression model to the original population of patients with stage IA and IC1 epithelial OvCa [18]. Independent variables that could be associated with prognosis of patients were clinically and statistically considered; therefore, we selected the following independent variables: age, cancer antigen (CA)-125 levels, the year of diagnosis, histology, ascites volume, uterine preservation, full-staging lymphadenectomy, and adjuvant chemotherapy. When creating PS, missing values were substituted with each average variable number. We adjusted cohorts with the inverse probability weighting of the treatment approach; each individual was weighted by the inverse probability of undergoing pelvic and para-aortic lymphadenectomy, equal to 1/PS for treated individuals and 1/(1–PS) for control individuals [19]. Comparisons between the groups were analyzed using the Student's t-test for continuous variables and the χ^2 or Fisher's exact test for categorical variables, where appropriate. Kaplan-Meier curves with the inverse probability weighting of treatment adjustments were created to compare recurrence-free survival [20]. The Log-rank test was used to confirm differences in survival between the 2 groups. Cox's regression analyses were also performed to evaluate each predictor of recurrence-free survival in the original populations. As a subgroup analysis, the adjusted estimation of the HR for stage IC1 over

IA was also investigated with the stratification of each variable. In the subgroup analysis, PS was calculated using variables other than those that were used in each subgroup category. Significance was selected as 2-sided with a p-value <0.05. All statistical analyses were conducted using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Baseline characteristics of patients

A total of 4,730 patients with malignant ovarian tumors were originally included during the study period. Among 2,920 patients with epithelial OvCa, 658 (22.5%) were diagnosed with stage I disease; 245 with stage IA and 289 with stage IC1, respectively. The baseline characteristics of patients are shown in **Table 1**. Clear-cell carcinoma was the most common histology in both groups. More patients with stage IC1 tumors underwent hysterectomy, full-staging lymphadenectomy, and adjuvant chemotherapy than those with stage IA tumors.

2. Factors affecting the surgical spill of primary OvCa tumors

The impact of pre-operative clinical factors that may affect surgical spill was assessed according to odds ratios (ORs) in all patients (**Table 2**). A clear-cell histology was strongly associated with the capsule rupture of tumors (OR=2.145; 95% confidence interval [CI]=1.142–4.030; p=0.018). A high CA-125 level was also identified as a significant risk factor for surgical spill (OR=1.150; 95% CI=1.027–1.289; p=0.016), while other characteristics, including age, the year of diagnosis, and ascites volume, were not.

Table 1. Baseline characteristic of patients in the 2 groups

Categories	Stage IA (n=245)	Stage IC1 (n=289)	p-value
Age (yr)	51.1±13.8	52.5±12.1	0.020
Year of diagnosis			0.246
Before 1999	80 (32.7)	81 (28.0)	
After 2000	165 (67.3)	208 (72.0)	
Histology			<0.001
Serous	25 (10.2)	23 (8.0)	
Clear-cell	75 (30.6)	148 (51.2)	
Mucinous	75 (30.6)	44 (15.2)	
Endometrioid	64 (26.1)	69 (23.9)	
Others	6 (2.4)	5 (1.7)	
Tumor marker (IU/mL)			
CA-125	345.6±1,589.8	627.2±4,649.9	0.015*
CA-19-9	1,165.1±4,791.9	2,665.6±34,631.1	0.646*
CA-72-4	55.3±411.2	22.8±61.3	0.179*
CEA	12.2±65.6	33.9±359.4	0.812*
Surgical procedure			
Uterine-preserved	52 (21.2)	42 (14.5)	0.043
Full-staging lymphadenectomy	104 (42.4)	147 (50.1)	0.052
Ascites volume (mL)			0.001
<500	202 (82.4)	249 (86.2)	
≥500	34 (13.9)	27 (9.3)	
Adjuvant chemotherapy	106 (43.3)	251 (86.9)	<0.001

Data are presented as mean±standard deviation or number (%). Student's t-test, χ^2 test, or Fisher's exact test was used as appropriate.
CA, cancer antigen; CEA, carcinoembryonic antigen.
*Logarithmically transformed when analyzed.

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Table 2. OR for surgical spill of capsulated tumor in each factor of all patients

Categories	OR (95% CI)	p-value
Age	1.008 (0.995–1.022)	0.224
Year of diagnosis		
Before 1999	Reference	
After 2000	1.245 (0.860–1.803)	0.246
Histology		
Serous	Reference	
Clear-cell	2.145 (1.142–4.030)	0.018
Mucinous	0.638 (0.324–1.256)	0.193
Endometrioid	1.172 (0.605–2.269)	0.638
Others	0.906 (0.243–3.374)	0.883
Tumor marker		
CA-125	1.150 (1.027–1.289)*	0.016*
Ascites volume (mL)		
<500	Reference	
≥500	0.644 (0.376–1.104)	0.109

CA, cancer antigen; CI, confidence interval; OR, odds ratio.
*Logarithmically transformed when analyzed.

3. HR of recurrence in factors for PS adjustments

We primarily selected the following clinical factors that potentially influenced surgical spill and the survival outcomes of patients: age, CA-125 levels, the year of diagnosis, histology, ascites volume, uterine preservation, full-staging lymphadenectomy, and adjuvant chemotherapy. As shown in **Fig. S1** and **Table S1**, a secondary analysis was performed to determine the effect of each factor on survival outcomes. A serous histology indicated poorer recurrence-free survival than the other histologies (Log-rank test: p<0.001). A high CA-125 level significantly increased the risk of tumor recurrence (OR=1.160; 95% CI=1.044–1.288; p=0.006). On the other hand, incomplete surgery, including uterine preservation and incomplete-staging lymphadenectomy, and post-operative chemotherapy alone did not correlate with recurrence-free survival.

4. Impact of surgical spill on tumor recurrence

With PS-based inverse probability of treatment weighting adjustments, the numbers of stage IA (n=245) and stage IC1 (n=289) patients in the original cohort increased by 532.8 and 541.7, respectively. The p-value for the Hosmer-Lemeshow test was 0.546 and the c-statistic of the PS model was 0.760. Adjusted Kaplan-Meier curves were shown in **Fig. 1A**, and revealed that patients with stage IC1 tumors had significantly worse recurrence-free survival than those with stage IA tumors (Log-rank test: p=0.005). Estimated 10-year recurrence-free survival rates were 79.7% (standard error [SE]=1.9%) and 72.8% (SE=2.0%) for patients with stage IA and IC1 tumors, respectively. In terms of the site of recurrent tumors (**Fig. 1B**), no significant differences were observed between the 2 groups (χ^2 test: p=0.072).

5. Subgroup analysis

We estimated the relative HR of recurrence with the surgical spill of capsulated tumors in adjusted cohorts for uterine preservation, full-staging lymphadenectomy, and adjuvant chemotherapy (**Fig. 2A**). Uterine preservation and incomplete-staging lymphadenectomy significantly increased the HR of recurrence with the surgical spill of tumors (uterine preservation: HR=1.669; 95% CI=1.052–2.744; p=0.003; incomplete-staging lymphadenectomy: HR=1.689; 95% CI=1.211–2.355; p=0.002). However, uterine preservation and incomplete-staging lymphadenectomy did not affect the prognosis of patients in the other subgroups. On the other hand, the omission of adjuvant chemotherapy (HR=3.729; 95% CI=2.090–6.653; p<0.001) markedly increased the risk of recurrence with surgical spill, while its inclusion decreased the impact of rupture.

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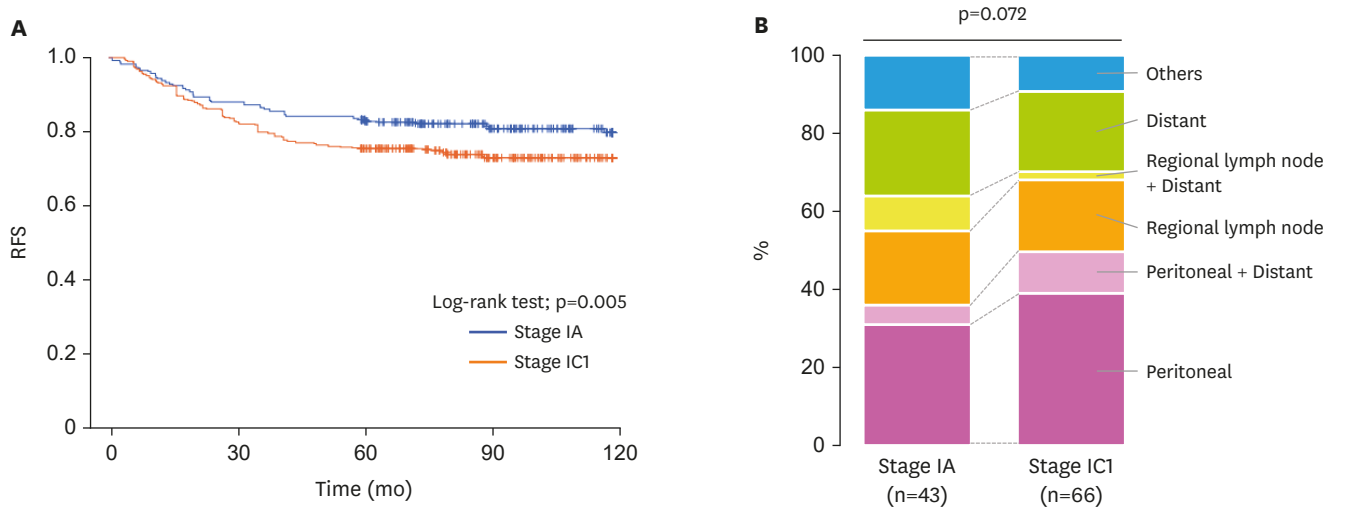

Fig. 1. (A) Propensity score-adjusted Kaplan-Meier curves for RFS in patients with stage IA and IC1 epithelial ovarian cancer. The p-values were estimated using the Log-rank test. (B) Percentage of patients with stage IA and IC1 epithelial ovarian cancer by the site of recurrence. The p-values were estimated using the χ^2 test.
RFS, recurrence-free survival.

A

Subgroup	Hazard Ratio (95% CI)	Ruptured	Not ruptured
All	1.445 (1.114–1.874)	68 / 289	45 / 245
Uterine-preservation			
Yes	1.669 (1.052–2.744)	12 / 42	11 / 52
No	1.258 (0.919–1.721)	56 / 247	34 / 193
Full-staging lymphadenectomy			
Yes	1.102 (0.722–1.683)	31 / 147	16 / 104
No	1.689 (1.211–2.355)	37 / 142	29 / 141
Adjuvant chemotherapy			
Yes	0.979 (0.697–1.375)	55 / 251	25 / 106
No	3.729 (2.090–6.653)	9 / 22	13 / 104

B

Subgroup	Hazard Ratio (95% CI)	Recurrence / Number	
Uterine-preservation: Yes			
Adjuvant chemotherapy: Yes	0.159 (0.230–1.168)	6 / 29	7 / 23
Adjuvant chemotherapy: No	3.226 (1.354–7.687)	6 / 11	4 / 22
Full-staging lymphadenectomy: No			
Adjuvant chemotherapy: Yes	0.987 (0.638–1.527)	28 / 118	18 / 66
Adjuvant chemotherapy: No	2.832 (1.491–5.378)	7 / 14	10 / 60

Fig. 2. (A) Propensity score-adjusted estimation of the HR of recurrence and 95% CI for the intraoperative rupture of capsulated tumors in each subgroup of patients with or without uterine preservation, full-staging lymphadenectomy, and adjuvant chemotherapy. (B) Subgroup analysis of patients with uterine preservation with or without adjuvant chemotherapy and incomplete-staging lymphadenectomy with or without adjuvant chemotherapy. Propensity scores in the subgroup analysis were calculated using variables other than those that were used in each subgroup category.
CI, confidence interval; HR, hazard ratio.

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In another subgroup analysis, we investigated whether adjuvant chemotherapy affected the poorer prognosis associated with incomplete surgery (**Fig. 2B**). As speculated, in both subgroups composed of patients with uterine preservation and incomplete-staging lymphadenectomy, the omission of adjuvant chemotherapy significantly increased the risk of recurrence with surgical spill, while its inclusion decreased the impact of rupture (uterine preservation: HR=13.226; 95% CI=1.354–7.687; p=0.008; incomplete-staging lymphadenectomy: HR=2.832; 95% CI=1.491–5.378; p=0.001).

DISCUSSION

In the present study, the impact of incomplete surgery for the intraoperative rupture of capsulated stage I epithelial OvCa was investigated with statistical adjustments for background clinical factors. The results obtained revealed that uterine preservation, incomplete-staging lymphadenectomy, and the omission of adjuvant operative chemotherapy increased the risk of tumor recurrence with capsule rupture. When chemotherapy is given for patients receiving uterine preservation or incomplete-staging lymphadenectomy, there is no longer an increased risk of recurrence observed with surgical rupture. Collectively, the present results suggest that adjuvant chemotherapy needs to be included in the treatment of patients with stage IC1 epithelial OvCa.

Previous studies reported the prognostic effects of surgical spill in stage I OvCa [10-13]. With the redefinition of FIGO staging in 2014, intraoperative rupture was categorized as stage IC1 from stage IA capsulated tumors [9]. The present results suggest that patients with stage IC1 tumors had a significantly worse prognosis than those with stage IA tumors. We also found that some clinical characteristics were associated with the intraoperative rupture of capsulated stage I epithelial OvCa. A logistic regression analysis revealed that a clear-cell histology and high CA-125 level correlated with surgical spill. This may be because a factor leading to capsule rupture, such as adhesion caused by endometriosis, already existed before surgery. Therefore, gynecologists need to consider the risk of surgical spill as well as peri- and post-operative therapeutic management for these patients.

The present study highlighted the importance of adjuvant chemotherapy for the intraoperative rupture of capsulated stage I OvCa. Previous studies reported the necessity of adjuvant chemotherapy for stage IC1 disease. Matsuo et al. [13] recently examined the effects of intraoperative capsule rupture in a large number of stage I epithelial OvCa patients. The findings obtained revealed that adjuvant chemotherapy did not exert beneficial effects on the cause-specific survival of stage IC1 patients. Alternatively, a meta-analysis performed by Kim et al. [12] showed no significant differences in progression-free survival between intraoperative rupture and no rupture in patients who underwent complete surgical staging and received adjuvant platinum-based chemotherapy. On the other hand, according to primary practical guidelines, adjuvant chemotherapy may be omitted for patients with stage IA or IB/grade 1 tumors [6-8]. In our adjusted subgroup analysis, the omission of adjuvant chemotherapy was associated with the largest risk of recurrence with capsule rupture, and decreased the prognostic impact of incomplete surgery, which needs to be recognized as an important clinical effect. Incomplete surgery is inevitable under specific clinical conditions, such as young patients hoping for future pregnancy or elderly patients with comorbidities. Since we adjusted for background factors, including age, histology, tumor markers, and ascites volumes, the results obtained on survival outcomes may be interpreted as being independent from these clinical factors. The feasibility

of adjuvant chemotherapy for stage IC1 epithelial OvCa needs to be confirmed in further trials, including Japanese Gynecologic Oncology Group 3020, prospectively investigating the effectiveness of adjuvant chemotherapy for each substage of stage I epithelial OvCa [21].

The strength of the present study was that data were obtained from multiple affiliated institutions under a central pathological review. Based on this system, the principle therapeutic strategy was consistently managed, including the surgical procedure performed and administration of chemotherapy. We also adjusted for imbalances in the 2 groups with PS-based statistical methods, which increased the robustness of the results obtained. On the other hand, the limitations included the potential existence of confounding factors, such as the performance status of patients. Due to the retrospective design of the present study, the results obtained need to be validated in future trials.

In conclusion, the intraoperative rupture of capsulated stage I epithelial OvCa is associated with a poor prognosis. When chemotherapy is given for patients receiving uterine preservation or incomplete-staging surgery, there is no longer an increased risk of recurrence observed with surgical rupture.

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SUPPLEMENTARY MATERIALS

Table S1

Hazard of recurrence in each factor for PS-adjustment

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Fig. S1

Kaplan-Meier curves for recurrence-free survival stratified by (A) the year of diagnosis, (B) histology, (C) ascites volume, (D) uterine preservation, (E) full-staging lymphadenectomy, and (F) adjuvant chemotherapy. The p-values were estimated using the Log-rank test.

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