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Poor prognosis of ovarian cancer with large cell neuroendocrine carcinoma: Case report and review of published works

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Abstract

Large cell neuroendocrine carcinoma (LCNEC) is well-reported to result in unfavorable prognoses in many organ cancers while being rarely reported in gynecologic cancer, especially ovarian and endometrial cancers. Here we report a case of ovarian cancer with LCNEC which spread to distant organs within 1 year of primary surgery despite the fact that the post-surgical stage was Ia. The case received platinum-based chemotherapy as an adjuvant therapy after her curative surgery. However, LCNEC in the case was resistant to the chemotherapy. In our review of published works, ovarian cancer cases with LCNEC show poor prognoses regardless of adjuvant chemotherapy following complete resection. Median overall survival was 10 months in stage I cases. Development of chemotherapy sensitive for LCNEC is needed.

Key words: chromogranin A, gynecologic cancer, large cell neuroendocrine carcinoma, ovarian cancer, platinum-based chemotherapy.

Introduction

Large cell neuroendocrine carcinoma (LCNEC) is synonymous with 'undifferentiated carcinoma of non-small cell neuroendocrine type' and defined as 'a malignant tumor composed of large cells that show neuroendocrine differentiation'.[1] However, there exist no generally accepted criteria for neuroendocrine tumor differentiation, which usually depends on a combination of typical structural, immunohistochemical and ultrastructural findings. World Health Organization (WHO) criteria describe that LCNEC of the lung is characterized by positive immunostaining for chromogranin A, synaptophysin or CD56 (N-CAM) and at least one of them is enough if the staining is clear cut.[2] LCNEC of the ovary is very rare and only 35 cases have been reported previously worldwide.[2–17] Its prognosis is generally very poor, even when the diagnosis is made at an early stage. We experienced a case of LCNEC of the ovary who died of disseminated disease within 7 months after the primary surgery despite extensive surgery and adjuvant chemotherapy.

Case Report

A 50-year-old woman, gravida 3 para 2, presented with abdominal distension for 1 month. Physical

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examination revealed a firm mass in the lower abdomen that was equivalent to the head of a newborn infant. Ultrasonographic tomography, magnetic resonance imaging and computed tomography (CT) demonstrated a monolocular cyst measuring 15 cm × 12 cm × 10 cm in diameter in the abdominal cavity. Abdominal organs were otherwise normal and the lungs were normal. Preoperative serum level of carbohydrate antigen (CA)125, CA19-9, carcinoembryonic antigen, α-fetoprotein and lactate dehydrogenase were within normal ranges. A smooth-surfaced right ovarian tumor was found at laparotomy. The uterus, tubes, left ovary and omentum were normal and no other tumor was evident in the abdominal cavity. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic lymphadenectomy were performed. A smooth round tumor 15 cm in diameter was resected without rupture. In the tumor wall, several thickened lesions were seen (Fig. 1a, arrowhead). Hematoxylin–eosin staining of the tumor revealed microscopically mucinous epithelium lining the inside of the tumor wall and several parts relevant to the thickened lesions were composed of poorly differentiated large cells forming a front of the normal mucinous epithelium (Fig. 1b,c). To assess features of the large cells, immunohistochemistry was performed. Positivity for CD56, chromogranin A, synaptophysin and neuron-specific enolase (NSE) demonstrated the large cells were neuroendocrine components (Fig. 1d–g). Taken together, the ovarian tumor was classified as LCNEC associated with mucinous adenoma. Remarkable vascular invasion was observed in the tumor wall, especially around the thickened lesions.

She was diagnosed as having ovarian cancer of stage Ia (pT1aN0M0) of LCNEC associated with mucinous adenoma and received EP (cisplatin 75 mg/m^2 and etoposide 100 mg/m^2 once a day for 5 days) as an adjuvant chemotherapy. However, multiple liver metastases were detected by CT at 4 months after her primary operation when she received three rounds of EP. Then, her chemotherapy regimen was changed to TC (paclitaxel 175 mg/m^2 and carboplatin AUC 6) or CPT-11 (90 mg/m^2) alone as second- or third-line chemotherapy, respectively. Clinical responses to any regimen were not observed in this case. Her cancer was thought to be refractory for any regimen and progressed rapidly. Unfortunately, she died of progressive disease only 7 months after her primary operation.

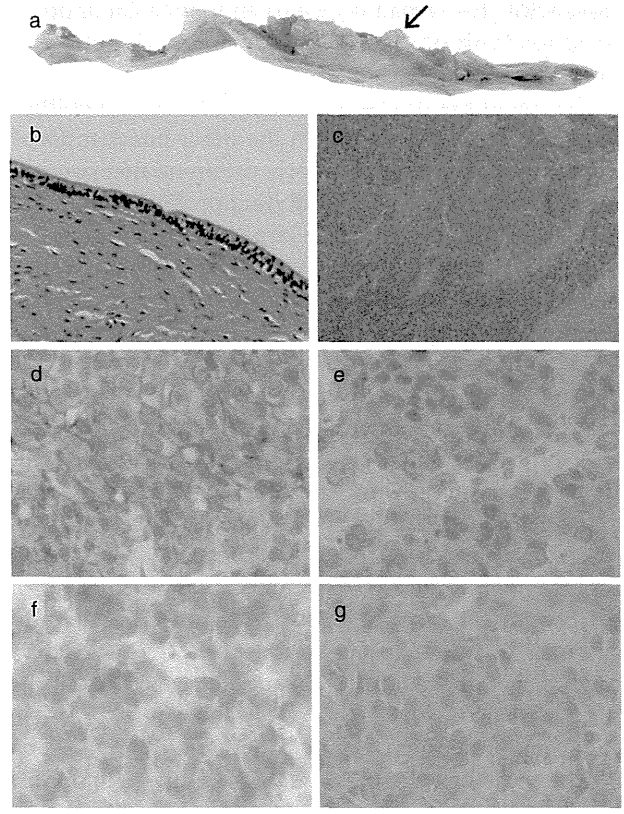

Figure 1 Pathological and immunohistochemical findings of this case. (a) Macroscopic finding: the cut surface of the right ovary was smooth. Several thickened lesions were seen in the tumor wall (arrow). (b) Microscopic finding (hematoxylin–eosin [HE] staining): mucinous epithelium lined inside of the tumor wall (original magnification, ×100). (c) Microscopic finding (HE staining): poorly-differentiated large cells in several parts relevant to the thickened lesions (×40). (d–g) Immunohistochemical studies of this case for representative neuroendocrine markers: CD56 (d: ×400), chromogranin A (e: ×400), synaptophysin (f: ×400) and neuron-specific enolase (g: ×400).

Discussion

Large cell neuroendocrine carcinoma of the ovary is included in the WHO tumor classification. To date, 35 cases of ovarian LCNEC have been reported in the published work. Thirty-three cases received an operation and been diagnosed postoperatively as ovarian LCNEC. These included 16 cases of stage I, three cases of stage II, eight cases of stage III and six cases of stage IV. Most of these cases seem to be associated with benign ovarian epithelial neoplasms. Of 33 cases, pure neuroendocrine carcinoma accounted for only four

cases while the remaining neuroendocrine carcinomas coexisted with ovarian epithelial tumors or germ cell tumors.

The tumor in our case was lined with benign epithelium mucinous adenoma. On the other hand, most of the tumor consisted of a poorly differentiated component of large tumor cells exhibiting proliferation in the thickened wall. Nuclei were large and had prominent nucleoli. Vascular invasion was prominent. Immunohistochemistry revealed that the cells of the poorly differentiated component were diffusely positive for CD56, chromogranin A, synaptophysin and NSE. Taken together, the tumor fulfilled the histopathological criteria for a neuroendocrine carcinoma.[2]

A high frequency of vascular invasion has been reported in neuroendocrine carcinomas of the lung and other sites.[18] In terms of gynecologic cancer, vascular invasion in LCNEC of the cervix has been reported to be much more common than in other types of cervical carcinomas.[19] Our case showed a definite vascular invasion at the lesions of LCNEC, which might have resulted in the distant metastasis in spite of the early stage.

Large cell neuroendocrine carcinoma in any organs is thought to be an aggressive tumor with high mortality despite extensive surgery and adjuvant chemotherapy. In our case, LCNEC spread to distant organs within 1 year after primary surgery despite the fact that the post-surgical stage was Ia and adjuvant chemotherapy was performed. However, one report mentions that cases of ovarian LCNEC, particularly those of stage I and/or those who have received platinum-based therapy, may have a favorable prognosis.[13] Then, we addressed the overall survival rate with ovarian LCNEC of stage I by Kaplan–Meier curve based on the published works (Fig. 2). Overall survival was available in 15 previously reported cases, with a median follow-up period of 9 months (including our study). Among these 16 cases, nine died of the disease within 3–19 months after primary operation and the remaining seven patients were alive at follow-up periods ranging 6–120 months. The median overall survival was 10 months and 1-year overall survival rate was 47.1% on the Kaplan–Meier curve. This suggests that the LCNEC of the ovary has a very poor prognosis even at stage I.

Veronesi *et al.* reported a series of 144 cases of lung LCNEC who received debulking surgery. Of them, 21 and 24 cases received neoadjuvant or postoperative adjuvant chemotherapy, respectively, and response rate of the chemotherapy was 80% in 15 cases with data

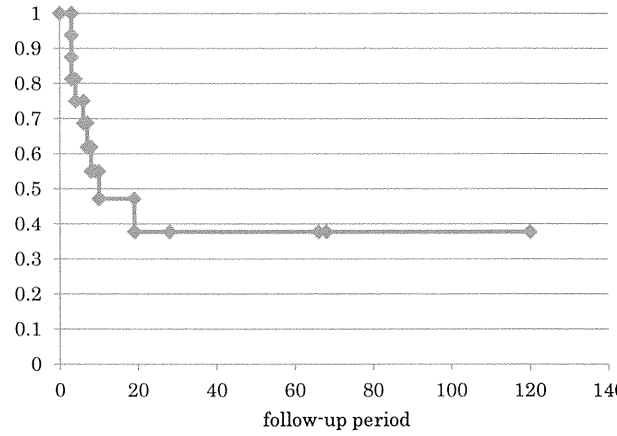

Figure 2 Kaplan–Meier curve of overall survival for ovarian large cell neuroendocrine carcinoma stage I. This case and 15 cases reported as stage I in the published work are summarized. One-year overall survival of these cases was 47.1% by Kaplan–Meier method. —◆—, survival rate.

available. They demonstrated that combination of chemotherapy and surgery improved overall survival of the lung LCNEC stage I with marginal significance when compared with surgery alone.[20] Another group also reported that two cases of lung stage I LCNEC who received cisplatin and etoposide combination chemotherapy survived for 2 and 5 years after complete pulmonary resection, respectively.[21] These data allowed for a possibility that platinum-based adjuvant chemotherapy after curative surgery may result in relatively long survival of the lung LCNEC cases of early stage. These rationales encouraged us to add combination adjuvant chemotherapy of cisplatin and etoposide to our case. However, our case died of disseminated disease within 7 months of the primary surgery. Chemosensitivity of the ovarian LCNEC to platinum-based chemotherapy may be lower than that of the lung LCNEC. Additional cases of this carcinoma will have to be collected to establish optimal adjuvant chemotherapy.

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ORIGINAL ARTICLE

The safety and efficacy of cisplatin plus gemcitabine in recurrent ovarian cancer

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Abstract
Background The activity and synergy for the combination treatment of cisplatin and gemcitabine has been identified in a variety of human tumor cells, including ovarian cancer cells, and has been widely approved for the treatment of non-small cell lung cancer, pancreatic cancer and biliary tract cancer. As the gastrointestinal symptoms with cisplatin therapy are commonly considered to negatively affect the quality of life of patients more than those experienced with carboplatin therapy, carboplatin is generally preferred over cisplatin in combination therapy. This study evaluated the safety and efficacy of cisplatin plus gemcitabine in patients with recurrent ovarian cancer.
Methods Patients with recurrent ovarian, peritoneal or fallopian tube cancer, who had failed with multiple other chemotherapy agents, including platinum, received cisplatin (30 mg/m^2) plus gemcitabine (750 mg/m^2) on days 1 and 8 of every 28 days for between 1 and 4 cycles.
Results In total, 18 patients were treated with cisplatin and gemcitabine between 2006 and 2011. There were 1 complete and 5 partial responses, producing an overall response rate of 33.4 %. Median overall survival was 11.0 months. Grade 4 neutropenia and thrombocytopenia were seen in 11.1 and 22.2 % of patients, respectively. Non-hematological toxicity was less than Grade 1.
Conclusions Non-hematological toxicity with combined cisplatin and gemcitabine therapy was considered tolerable and did not impede patient quality of life. However, this drug combination should be monitored for hematologic toxicity.

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Keywords Recurrent ovarian cancer · Cisplatin · Gemcitabine · Platinum resistant · Platinum sensitive

Introduction

Many patients with ovarian cancer are diagnosed when the disease has reached an advanced stage. Most will relapse after initial treatment and their prognosis will be poor [1]. The mainstay of treatment of recurrent ovarian cancer is chemotherapy; however, a majority of patients are resistant to therapy. Thus, one of the main purposes of treatment is palliative care, if possible obtaining a survival benefit for the patient, while maintaining their quality of life. Management of recurrent ovarian cancer has involved numerous second-line agents. Gemcitabine (GEM), for example, is a deoxycytidine nucleotide analog of cytosine arabinoside, which has been studied as a single agent in ovarian cancer and has demonstrated response rates of 15–20 % [2]. Cisplatin (CDDP) is among the most widely used antineoplastic drugs and has broad clinical activity. Since its introduction in the 1970s, it has become a mainstay in the management of advanced ovarian cancer. Clinical "platinum-resistance" is widely recognized as a major prognostic factor in ovarian cancer outcome [3, 4].

Gemcitabine has been shown to enhance the activity of cisplatin by increasing platinum-induced DNA adduct formation and by inhibiting the activity of the excision repair gene, ERCC1, which deranges an important mechanism of platinum resistance. Examination of the interaction between cisplatin and gemcitabine in a variety of human tumor cells, including ovarian cancer cells, has identified activity and synergy for the combination [3–5], which has been widely approved for the treatment of non-

small cell lung cancer, pancreatic cancer and biliary tract cancer [4, 6, 7].

A randomized controlled trial (AGO-OVAR) of single agent and combination chemotherapy for platinum-sensitive recurrent ovarian cancer was conducted in 2005. This study demonstrated that patients receiving combination therapy (carboplatin/gemcitabine) had longer progression-free survival (PFS) than the patients receiving just carboplatin [8]. As the gastrointestinal symptoms with cisplatin therapy are commonly considered to negatively impact the quality of life of patients more than those experienced with carboplatin therapy, carboplatin is generally preferred over cisplatin in combination therapy. However, supportive care options can suppress the cisplatin gastrointestinal symptoms sufficiently for the combination of cisplatin and gemcitabine to be considered. Cisplatin is associated with less bone marrow suppression (a recognized issue with second-line therapy) than carboplatin.

The combination of cisplatin and gemcitabine was employed for second- and third-line treatment in patients with recurrent ovarian cancer. The purpose of this study was to examine the clinical efficacy and toxicity of this regimen and to prove that this novel combination is a therapeutic option for patients with recurrent ovarian cancer.

Materials and methods

Eligibility criteria

We performed a retrospective review of patients with recurrent ovarian or peritoneal or fallopian tube cancer. Patients who had been unsuccessfully treated with multiple other agents, including platinum, were treated with the combination of cisplatin and gemcitabine in Kyushu Cancer Center. All patients had bidirectional disease measurable by physical examination or medical imaging (CT, MRI), had not been previously treated with gemcitabine, and had an Eastern Cooperative Oncology Group performance status 0, 1, 2. Patients were defined as platinum resistant if they progressed on or within 6 months of the most recent platinum regimen. Those with concomitant or prior malignancy within the preceding 5 years were not eligible for this study, nor were those with active infection, clinical congestive heart failure, hypoxemia, and concurrent radiation or hormonal therapy. Informed consent was obtained from all patients before enrollment.

Chemotherapy

Treatment consisted of cisplatin 30 mg/m^2 administered intravenously over 2 h followed by gemcitabine 750 mg/m^2 over 30 min, given on day 1 and 8 every 28 days. The dosages of the drugs were decided according to the protocol reported by Nagourney and Rose [4, 9]. For the first occurrence of neutropenic fever or prolonged grade 4 neutropenia or grade 4 thrombocytopenia, the gemcitabine dose was reduced to 600 mg/m^2 for the following courses, at the physician's discretion. If similar hematologic toxicity appeared after the following courses, the gemcitabine dose was further reduced to 75 or 50 %. Therapy was administered if the absolute neutrophil count was >1500/μl and platelets were >100000/μl. Day 8 therapy was cancelled if the absolute neutrophil count was <1000/μl or the platelet count was <75000/μl. Prophylactic G-CSF formulation was used when grade 4 neutropenia was seen in patients who had been previously treated with radiotherapy.

Criteria for response

The progress of the disease was evaluated after each course of treatment, and each course (between 1 and 4 courses) was administered at the discretion of the treating physician. Evaluation of disease progress was made using standard response evaluation criteria in solid tumors (RECIST) [10]. A complete response (CR) was defined as the disappearance of all measurable disease. A partial response (PR) was defined as a 30 % or greater reduction in the products of each measurable lesion. Progressive disease (PD) was defined as a 20 % or more increase in the products of any indicated lesion or the appearance of any new lesions. Stable disease was defined as any condition not meeting any of the above criteria. No evaluation (NE) was used if the examination was not performed. Adverse events were evaluated based on the common terminology criteria for adverse events (CTCAE) Version 4.0.

Statistical analysis

Progression free survival was defined as the period from the start of therapy until disease progression or the last date of contact. Analyses were performed using Statistical Package for Social Sciences (SPSS®) software, version 11 (SPSS Inc, Chicago, IL, USA). Survival curves were calculated using Kaplan–Meier survival analyses. Fisher's exact test was used for evaluating the difference of response rate between 2 groups.

Results

In total, 18 women with a recurrent ovarian, peritoneal, or fallopian tube carcinoma were treated with a combination of cisplatin and gemcitabine between January 2006 and

October 2011. Patient characteristics are shown in Table 1. The median age of this group was 62 years and all had excellent performance statuses with ECOG/WHO scores <2. Before receiving the study treatment, these patients had received a median of 2.5 (range 1–4) chemotherapy regimens and five patients had received radiation therapy. Fifteen patients had received multiple platinum-based regimens. Ten of the 18 patients (55.6 %) met the Gynecologic Oncology Group criteria [11] for platinum sensitivity and 8 of the 18 patients (44.4 %) met the criteria for platinum resistance. The median number of chemotherapy cycles administered was 3.

Of the 18 patients, 16 were evaluable for response. Two patients experienced severe thrombocytopenia after first course of treatment, and were forced to change treatment. These 2 patients did not have adequate examination for response and were defined to be not evaluable for response.

Table 1 Characteristics of patients ($n = 18$) with recurrent ovarian, peritoneal or fallopian tube cancer

Characteristic	Number of cases
Age	
Median	61.9
Range	44–78
FIGO stage at initial diagnosis	
I	1
II	2
III	14
IV	1
Differentiation	
Serous	9
Endometrioid	2
Clear cell	1
Carcinosarcoma	1
Undifferentiated	5
Prior chemotherapy	
Median	2.5
Range	1–4
Platinum sensitive	10
Resistant	8

Six patients (33.3 %) responded to the treatment, 5 (27.8 %) had a partial clinical response and one patient (5.6 %) had a complete response (Table 2). The response rate of platinum sensitive cases tended to be higher than that of platinum resistance cases without statistical significance ($p = 0.1516$). Interestingly, the only one case with complete remission was a platinum-resistance case. For all patients, the median progression-free survival time was 3.5 months(95 %CI 1–11 months) and the median survival time was 11 months (95 % CI 7–15 months) (Fig. 1).

Significant toxicities associated with this combination therapy are listed in Tables 3 and 4. The most common adverse events were hematologic, with most treatments associated with either a grade 3 or 4 neutropenic or thrombocytopenic event [neutropenia grade 3 (44.4 %) and grade 4 (11.1 %); thrombocytopenia grade 3 (50 %) and grade 4 (22.2 %)]. During the course of treatment, 3 patients had grade 3 anemia, one patient received a red blood cell transfusion, and 3 patients received platelet transfusions. Other side-effects included nausea in 38.9 % of patients, vomiting in 11.1 %, fatigue in 22.2 %, and anorexia in 27.8 %, all of which were classified as <grade 1. Six patients required dose reductions for hematologic toxicities, 4 patients discontinued treatment [2 patients because of severe thrombocytopenia, one patient was allergic to cisplatin and one patient had increased serum creatinine levels (grade 2)]. There were no treatment related deaths.

Discussion

The purpose of this study was to examine the efficacy and safety of the combination therapy of cisplatin and gemcitabine, which has already been shown to be effective in different types of cancer. The Gynecologic Oncology Group reported a 16 % response rate in a phase II trial of cisplatin and gemcitabine in platinum-resistant patients with ovarian or peritoneal cancer in 2006 [3]; Rose et al. [9] reported a 43 % response rate in similar patients; Nagourney et al. [4] reported a 57 % response rate in a phase II trial in platinum-resistant patients with ovarian cancer

Table 2 Response to cisplatin plus gemcitabine treatment

Response	Platinum-sensitive ($n = 10$)	Platinum-resistant ($n = 8$)	Total ($n = 18$)
Complete response	0 (0 %)	1 (12.5 %)	1 (5.6 %)
Partial response	5 (50.0 %)	0 (0 %)	5 (27.8 %)
Stable disease	0 (0 %)	3 (37.5 %)	3 (16.7 %)
Progressive disease	4 (40.0 %)	3 (37.5 %)	7 (38.9 %)
Not evaluable	1 (10.0 %)	1 (12.5 %)	2 (11.1 %)
Total positive response	5 (50.0 %)	1 (12.5 %)	6 (33.3 %)

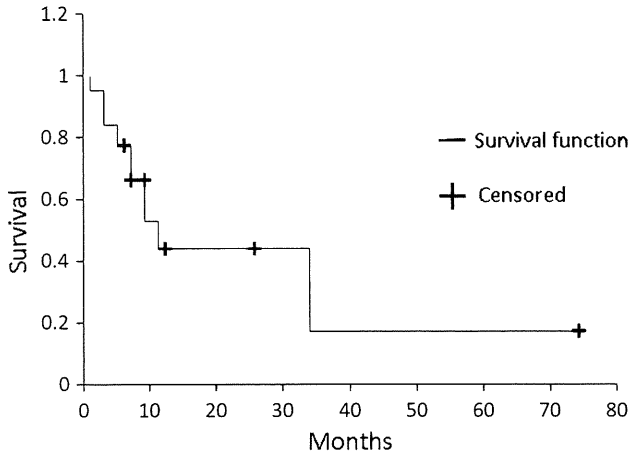

Fig. 1 Overall rate of survival for the 18 patients

Table 3 Hematologic adverse events

	Grade 3	Grade 4
Leukopenia	8 (44.4 %)	0
Neutropenia	8 (44.4 %)	2 (11.1 %)
Anemia	3 (16.7 %)	0
Thrombocytopenia	9 (50 %)	4 (22.2 %)

Table 4 Non-hematologic adverse events

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	7 (38.9 %)	0	0	0
Vomiting	2 (11.1 %)	0	0	0
Anorexia	5 (27.8 %)	0	0	0
Fatigue	4 (22.2 %)	0	0	0
Allergic reaction (CDDP)	0	1 (5.6 %)	0	0

and a 70 % response rate in patients where more than half of responses were in patients considered platinum-sensitive. Although the results in the current study varied from these reports, they all found the combination of cisplatin and gemcitabine to be effective. The difference in response rate between these studies may have been influenced by the time since patients had received prior platinum-containing therapy [3, 4, 6, 10, 11]. In the current study, the platinum-free interval and the level of platinum resistance was not measured; however, the response rate of 33.4 % was comparable to published reports and confirms this chemotherapy combination to be effective.

Hematologic toxicities were the most common adverse events in previous studies, and also in the current study [2–4, 6, 10, 11]. A previous study had tested the biweekly drug schedule and found reduced hematologic toxicity, without loss of clinical effectiveness [11]. Further reports have suggested that bone marrow suppression may be lessened by the order of administration of gemcitabine and cisplatin [2, 9]. Although this drug schedule requires further investigation, it seems to offer lower toxicity than other schedules with these agents, including a low level of gastrointestinal symptoms.

The mechanism of cisplatin gemcitabine synergism and their effect on platinum resistance has been extensively studied in vitro in ovarian cancer cells [5]. Platins remain the most important drugs for treating advanced ovarian cancer, and platinum resistance is one of the most important prognostic factors [4]. The combination of carboplatin and gemcitabine is becoming more commonly employed for platinum-sensitive recurrent ovarian cancer, particularly following the results of the AGO-OVAR study [8]. Hematologic and non-hematologic toxicities with the cisplatin and gemcitabine combination were comparable to those reported in the AGO-OVAR study [8]. This drug combination has also been found to be effective for platinum-resistant recurrent ovarian cancer. The limitation of the present study was obvious because of the retrospective nature. Base on the present findings, prospective phase 2 or 3 trial using the combination of cisplatin plus gemcitabine for ovarian cancer is warranted in Japan.

In conclusion, cisplatin plus gemcitabine may be a useful treatment strategy to prolong survival and provide palliative treatment in patients with recurrent ovarian cancer, and, although care regarding hematological toxicity must be taken with this combination, non-hematological toxicity is mild and patients retain quality of life.

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Conflict of interest The authors declare that they have no conflict of interest.

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Impact of Surgical Staging in Stage I Clear Cell Adenocarcinoma of the Ovary

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Aim: The aim of this study was to evaluate the impact of surgical staging in stage I clear cell adenocarcinoma of the ovary (CCC).

Methods: We performed a retrospective review of 165 patients with stage I CCC treated with optimal or nonoptimal staging surgery.

Results: The median follow-up period in this study was 67 months. No significant difference was detected in recurrence-free survival (RFS) or overall survival (OS) between patients optimally and nonoptimally staged (RFS: $P = 0.434$; OS: $P = 0.759$). The estimated 5-year RFS and OS rates were 92.1% and 95.3% in patients with stages IA/IC1 and 81.0% and 83.7% in stages IC2/IC3, respectively. The multivariate analysis indicated that stages IC2/IC3 predicted worse RFS and OS than stages IA/IC1 in stage I CCC patients (RFS: $P = 0.011$; OS: $P = 0.011$). Subsequently, we investigated the impact of surgical staging, respectively, in stages IA/IC1 and stages IC2/IC3. Significant differences were observed in PFS and OS between patients optimally and nonoptimally staged with stages IA/IC1 (RFS: $P = 0.021$; OS: $P = 0.024$), but no significant difference was found in those with stages IC2/IC3. The multivariate analysis indicated that nonoptimal staging surgery predicted worse RFS than the optimal staging surgery in stages IA/IC1 CCC patients ($P = 0.033$). In addition, we investigated the impact of surgical staging for stages IA/IC1 in the adjuvant chemotherapy group. The 5-year RFS and OS rates in patients optimally and nonoptimally staged with stages IA/IC1 in the adjuvant chemotherapy group were 97.8% and 100%, and 85.2% and 89.4%, respectively. The multivariate analysis indicated that nonoptimal staging surgery predicted worse RFS than the optimal staging surgery for stages IA/IC1 patients in the adjuvant chemotherapy group ($P = 0.019$).

Conclusions: The prognosis for women with stage 1A/IC1 is very good. Surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC.

Key Words: Ovarian cancer, Clear cell carcinoma, Surgical staging, Lymphadenectomy, Adjuvant chemotherapy

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Clear cell adenocarcinoma of the ovary (CCC) has been recognized as a distinct histologic entity under the World Health Organization classification of ovarian tumors since 1973. It is characterized by its association with endometriosis and frequent mutations of ARID1A and PIK3CA.[1] Clear cell adenocarcinoma of the ovary is the second most common type of epithelial ovarian cancer (EOC) in Japan, representing 23.7% of ovarian malignancies.[2] Women with CCC are more likely to present at a younger age, to be diagnosed with stage I to II disease, and have a poorer prognosis compared with serous adenocarcinoma.[3]

Trimbos et al[4] performed a preplanned combined analysis of 2 parallel randomized clinical trials (International Collaborative Ovarian Neoplasm 1 and European Organisation for Research and Treatment of Cancer–Adjuvant ChemoTherapy In Ovarian Neoplasm [EORTC-ACTION]) in early-stage EOC that compared platinum-based adjuvant chemotherapy with observation following initial surgery. Adjuvant chemotherapy improved overall survival (OS) and recurrence-free survival (RFS) at 5 years in patients with early-stage EOC.[4–6] The EORTC-ACTION trial was performed to test the efficacy of adjuvant chemotherapy for early-stage EOC, with emphasis on the extent of surgical staging.[5] Among the patients in the observation arm, optimal staging was associated with a statistically significant improvement in OS and RFS, whereas no such association was observed in the chemotherapy arm. In the nonoptimally staged patients, adjuvant chemotherapy was associated with statistically significant improvements in survival.[5] Furthermore, staging adequacy was an independent prognostic factor for survival.[5] It was concluded that the survival benefit of adjuvant chemotherapy was apparently limited to patients with nonoptimal surgical staging, that is, to patients who were at higher risk of unappreciated residual disease.[5] The proportion of patients with CCC was only 14%.[5]

A staging laparotomy is an important part of early management for EOC.[7] As outlined by the 1988 International Federation of Gynecology and Obstetrics (FIGO), recommended staging procedures include assessment for metastasis through biopsies of suspicious- and benign-appearing tissues in the abdominal cavity and within retroperitoneal lymphatic channels alongside pelvic and the para-aortic lymph bearing tissues.[8,9] The extent of lymphadenectomy (LNX) that is required to adequately presume early-stage EOC is not well defined.[9] The FIGO recommendations state that staging should include "selected LNX of the pelvic and para-aortic lymph nodes, at least ipsilateral if the malignancy is unilateral."[7] In fact, the optimal staging that was defined in EORTC-ACTION trial included only iliac and periaortic lymph node sampling, but that did not include systematic pelvic LNX (PEL-LNX) or para-aortic LNX (PAO-LNX). On the other hand, comprehensive staging surgery including PEL-LNX and PAO-LNX is recommended by several recent guidelines and often upstages women presumed to have early-stage disease.[10,11] It was reported that the mean incidences of lymph node metastases in clinical stage I-II EOC and CCC were 14.2% and 14.4%, respectively.[12]

To evaluate the impact of surgical staging in stage I CCC, we retrospectively reviewed outcomes in 165 stage I CCC patients who underwent optimal or nonoptimal surgical staging.

PATIENTS AND METHODS

Patients

Between 2000 and 2009, 165 patients with stage I CCC were identified by reviewing the medical records of the 4 hospitals affiliated to The Jikei University School of Medicine. A diagnosis of pure-type CCC was made in all these patients. Pure-type CCC was diagnosed as previously described.[13] Surgical staging was assessed according to FIGO (approved by the FIGO Executive Board in October 2012 and published in January 2014).[14] In the new FIGO classification, stage IC1 was defined as tumor limited to 1 or both ovaries with only intraoperative capsule rupture (no surface involvement and negative cytology), stage IC2 was defined as that with surface involvement or with preoperative capsule rupture (negative cytology), and stage IC3 was defined as that with malignant cells in the ascites or peritoneal washings.[14]

Surgical Staging

For surgical staging, upon entering the abdominopelvic cavity, the peritoneal fluid was taken for cytological examination (peritoneal fluid cytology). In the absence of ascites, irrigation was performed, and washings were taken for cytological examination (peritoneal washing cytology). Furthermore, surgical staging was consisted of at least examination to look for capsular rupture of ovarian tumor and careful inspection and palpation of all peritoneal surfaces, with biopsies of any suspected lesions, such as adhesions adjacent to the ovarian tumor. In addition, we defined 3 types of the surgical staging categories: optimal, minimal, and inadequate (Table 1). In addition, we defined nonoptimal staging surgery as minimal or inadequate staging surgeries. Surgeries with selected LNX of the pelvic and/or para-aortic lymph nodes belonged to minimal or inadequate staging surgery, but not to optimal. In principle, the choice between systematic and selected LNX in each patient was determined by the institutional treatment policy in staging surgery for presumed early-stage EOC at the time of surgery. The number of lymph nodes that were removed and pathologically examined was not considered for the completion of the LNX.

Adjuvant Chemotherapy

In 165 patients, 146 (88.5%) were treated postoperatively with the adjuvant chemotherapy: 96 (58.2%) with taxane plus platinum (TP), 46 (27.9%) with irinotecan hydrochloride plus cisplatin (CPT-P), 2 (1.2%) with conventional platinum-based chemotherapy, and 2 (1.2%) with irinotecan hydrochloride plus mitomycin C. Nineteen patients (11.5%) did not receive the adjuvant chemotherapy because of older age, the patients' wishes, or the decision of each institution.

Follow-Up and Analysis

At the end of treatment, all patients underwent regular follow-up, consisting of clinical checkups such as a pelvic examination, ultrasonographic scan, CA-125 evaluation, and periodic CT scan. Survival information was available on all patients. Overall survival was assessed from the date of initial surgery to the time of death or last contact. Recurrence-free

TABLE 1. Surgical staging categories

Surgical Staging Categories	Requirements for Surgical Staging
Optimal	Examination to look for capsular rupture of ovarian tumor; inspection and palpation of all peritoneal surfaces; biopsies of any suspected lesions; peritoneal fluid cytology or peritoneal washing cytology; total abdominal hysterectomy; bilateral salpingo-oophorectomy; subtotal (infragastroepiploic vessels) omentectomy; pelvic lymphadenectomy†; para-aortic lymphadenectomy‡
Minimal	Less than optimal staging but at least examination to look for capsular rupture of ovarian tumor; inspection and palpation of all peritoneal surfaces; biopsies of any suspected lesions; peritoneal fluid cytology or peritoneal washing cytology; total abdominal hysterectomy; bilateral salpingo-oophorectomy; infracolic or subtotal (infragastroepiploic vessels) omentectomy
Inadequate	Less than minimal staging but at least examination to look for capsular rupture of ovarian tumor; inspection and palpation of all peritoneal surfaces; biopsies of any suspected lesions; peritoneal fluid cytology or peritoneal washing cytology; unilateral salpingo-oophorectomy (eg, fertility-sparing surgery)

†Pelvic lymphadenectomy was the removal of the common, external, and internal iliac nodes and the obturator node groups to the level of the inguinal ligament.

‡Para-aortic lymphadenectomy was the removal of node-bearing tissues along aorta and vena cava to the level of the renal veins.

survival was defined as the time from initial surgery until recurrence or last contact. We designed the present study to evaluate the impact of surgical staging by the univariate and multivariate analyses in the whole sample for stage I CCC and in the 2 subgroups for stages IA/IC1 and stages IC2/IC3 separately because several previous reports revealed that CCC patients with stages IC2/IC3 showed poor RFS and OS than did those with stages IA/IC1.[15–17] Patient survival was calculated by using the Kaplan-Meier method, and the difference between groups was assessed by the log-rank test. The multiple Cox regression model was used to explore the impact of specific prognostic factors on OS and RFS. StatView software version 5.0 (SAS, Cary, NC) was used to analyze the data.

RESULTS

Patient Characteristics

In 165 patients, 80 were staged with optimal staging surgery, 74 with minimal staging surgery, and 11 with inadequate staging surgery. Median ages in patients optimally and nonoptimally staged were 52 years (range, 33–74 years) and 54 (range, 30-99 years), respectively ($P = 0.114$). Of the 80 optimally staged women, 13 were stage IA, 43 stage IC1, 6 stage IC2, and 18 stage IC3, whereas in the 85 nonoptimally staged women, 29 were stage IA, 43 stage IC1, 7 stage IC2, and 6 stage IC3 ($P = 0.007$). All 80 women optimally staged underwent systematic PEL-LNX and PAO-LNX, and 59 of 85 women nonoptimally staged underwent selected LNX. Meanwhile, 26 of 85 women nonoptimally staged did not receive LNX because of the patients' wishes or the decision of each institution ($P < 0.001$). Seventy-eight (97.5%) of 80 patients optimally staged and 68 (80.0%) of 85 nonoptimally staged were treated with adjuvant chemotherapy ($P = 0.001$) (Supplemental Digital Content Table: Patient Characteristics, http://links.lww.com/IGC/A222).

Prognostic Factors and Survival in All Stage I Patients

The median follow-up period in this study was 67 months (range, 3–148 months). Recurrence of disease was observed within and over 2 years after staging surgery in 5 and 2 of 80 patients optimally staged and 6 and 6 of 85 nonoptimally staged, respectively. In 1 patient optimally staged and 4 nonoptimally staged, first relapse occurred in the pelvic and/or para-aortic lymph nodes within 2 years after staging surgery. In addition, recurrence of disease was observed in 17 of 146 patients in the chemotherapy group and 2 of 19 in the observation group. One patient without recurrence died of leukemia.

The 5-year RFS and OS rates in 165 stage I patients by each category are summarized in Table 2. The significance of the RFS and OS distribution in each group as assessed by the log-rank test is also summarized in Table 2. In the whole population, no significant difference was detected in RFS or OS between patients optimally and nonoptimally staged (RFS: $P = 0.434$; OS: $P = 0.759$). There were significant differences in RFS and OS between patients with stages IA/IC1 and stages IC2/IC3 (RFS: $P = 0.017$; OS: $P = 0.012$) (Fig. 1). No significant difference was found in RFS or OS by age or adjuvant chemotherapy.

Multivariate analysis using the Cox regression model was performed to further assess the factors targeted, and the results are shown in Table 2. The analysis indicated that stages IC2/IC3 predicted worse RFS and OS than stages IA/IC1 (RFS: $P = 0.011$; relative risk [RR], 3.321; 95% confidence interval [CI], 1.313–8.403; OS: $P = 0.011$; RR, 4.202; 95% CI, 1.384–12.755). Stage was the only independent prognostic factor for RFS and OS in stage I CCC (Table 2).

Because the patients were treated with adjuvant chemotherapy more frequently in the optimally staged group (97.5%) than in the nonoptimally staged group (80.0%), we

TABLE 2. The recurrence-free and overall survival rates and relative risk of recurrent and death in all patients

Variable	Recurrence-free survival							Overall survival						
		Univariate analysis			Multivariate analysis				Univariate analysis			Multivariate analysis		
No. Patients	5-y Rate, %	Risk Ratio	95% CI	*P*-value	Risk Ratio	95% CI	*P*-value	5-y Rate, %	Risk Ratio	95% CI	*P*-value	Risk Ratio	95% CI	*P*-value
Age														
<50 years (n = 63)	91.1	1.367	0.558–3.412		1.606	0.651–3.966		91.1	1.273	0.433–3.794		1.503	0.505–4.470	
				0.484			0.304				0.653			0.464
≥50 years (n = 102)	87.3	1			1			97.5	1			1		
FIGO stage														
IA and IC1 (n = 128)	92.1	1			1			95.3	1			1		
IA (n = 42)	97.6							97.6						
IC1 (n = 86)	89.5							94.2						
				0.017			0.011				0.012			0.011
IC2 and IC3 (n = 37)	81.0	2.782	1.254–10.225		3.321	1.313–8.403		83.7	3.499	1.416–17.637		4.202	1.884–12.755	
IC2 (n = 13)	83.9							90.9						
IC3 (n = 24)	75.0							74.5						
Surgical staging category														
Optimal (n = 80)	92.5	1			1			93.7	1			1		
				0.434			0.197				0.759			0.463
Nonoptimal (n = 85)	87.0	1.427	0.489–3.419		1.856	0.726–4.746		91.7	1.179	0.412–3.367		1.527	0.494–4.724	
Minimal (n = 74)	87.8							91.9						
Inadequate(n = 11)	81.8							90.9						
Adjuvant chemotherapy														
Chemotherapy (n = 146)	89.7	1.129	0.279–4.530		1.169	0.262–5.220		92.4	1			1		
				0.870			0.838				0.723			0.642
Observation (n = 19)	89.4	1			1			94.7	1.309	0.257–7.067		1.443	0.307–6.775	

CI, Confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

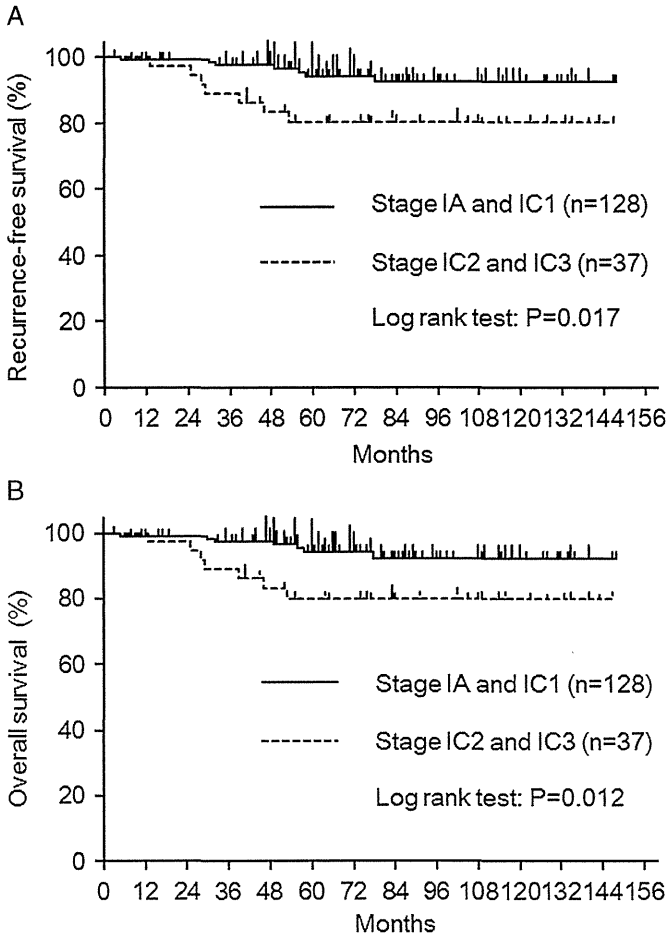

FIGURE 1. Kaplan-Meier curves for RFS (A) and OS (B) in patients with stages IA/IC1 and stages IC2/IC3. Significant differences were observed in RFS and OS between patients with stages IA/IC1 and stages IC2/IC3 (RFS: $P = 0.017$; OS: $P = 0.012$).

performed a subset analysis in patients treated with adjuvant chemotherapy. Among 146 patients who received adjuvant chemotherapy, no significant difference was observed in RFS or OS between patients optimally and nonoptimally staged (RFS: $P = 0.432$; OS: $P = 0.919$), aged <50 or ≥50 years (RFS: $P = 0.240$; OS: $P = 0.330$), or treated with TP and CPT-P (RFS: $P = 0.523$; OS: $P = 0.929$). There was a significant difference in RFS and OS between patients with stages IA/IC1 and stages IC2/IC3 (RFS: $P = 0.010$; OS: $P = 0.004$). The multivariate analysis indicated that stages IC2/IC3 predicted worse RFS and OS than stages IA/IC1 (RFS: $P = 0.008$; RR, 3.802; 95% CI, 1.423-10.152; OS: $P = 0.006$; RR, 5.470; 95% CI, 1.636–18.282). As a result, stage was the only independent prognostic factor for RFS and OS in the adjuvant chemotherapy group, whereas surgical staging category, age, or regimen of adjuvant chemotherapy was not.

Prognostic Factors and Survival in Patients With Stages IA/IC1

The 5-year RFS and OS rates in 128 stages IA/IC1 patients by each category are summarized in Table 3. The significance of the RFS and OS distribution in each group as assessed by the log-rank test is also summarized in Table 3. In patients with stages IA/IC1, significant differences were observed in PFS and OS between patients optimally and nonoptimally staged (RFS: $P = 0.021$; OS: $P = 0.024$; Fig. 2). No significant difference was found in RFS or OS by age, stage, or adjuvant chemotherapy.

Multivariate analysis using the Cox regression model for RFS was performed to further assess the factors targeted, and the results are shown in Table 3. The analysis indicated that nonoptimal staging surgery predicted worse RFS than the optimal staging surgery ($P = 0.033$; RR, 9.551; 95% CI, 1.194–76.355). As a result, surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC (Table 3). Multivariate analysis for OS could not be performed because of no event in patients optimally staged.

As with the analysis in the whole population, we added a subset analysis for the impact of surgical staging in patients with stages IA/IC1 in the adjuvant chemotherapy group. The 5-year RFS and OS rates were 97.8% and 100% in 55 stages IA/IC1 patients optimally staged and 83.3% and 91.7% in 56 stages IA/IC1patients nonoptimally staged, respectively (Fig. 3). Significant differences were observed in PFS and OS between patients optimally and nonoptimally staged (RFS: $P = 0.021$; OS: $P = 0.033$; Fig. 3), whereas no significant difference was observed in RFS or OS between patients younger than 50 years and those 50 years or older (RFS: $P = 0.290$; OS: $P = 0.329$), stage IA or IC (RFS: $P = 0.193$; OS: $P = 0.590$), and treated with TP or CPT-P (RFS: $P = 0.939$; OS: $P = 0.549$). The multivariate analysis indicated that nonoptimal staging surgery predicted worse RFS than the optimal staging surgery ($P = 0.019$; RR, 13.495; 95% CI, 1.543–117.647) for stages IA/IC1 patients in the adjuvant chemotherapy group. As a result, surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC patients treated with adjuvant chemotherapy, whereas age, stage, or regimen of adjuvant chemotherapy was not. Multivariate analysis for OS could not be performed because of no event in patients optimally staged.

Prognostic Factors and Survival in Patients With Stages IC2/IC3

In patients with stages IC2/IC3, no significant difference was observed in RFS or OS between patients optimally and nonoptimally staged (RFS: $P = 0.417$; OS: $P = 0.923$), patients younger than 50 years and 50 years or older (RFS: $P = 0.774$; OS: $P = 0.229$), or patients with stage IC2 and IC3 (RFS: $P = 0.623$: OS: $P = 0.196$). Survival differences between the adjuvant chemotherapy group and the observation group were not assessed because only 2 patients were in the observation group.

As with the analysis in patients with stages IA/IC1, we added a subset analysis for the impact of surgical staging in patients with stages IC2/IC3 in the adjuvant chemotherapy group. The 5-year RFS and OS rates were 73.0% and 72.1% in 23 stages IC2/IC3 patients optimally staged and 83.3% and 91.7% in 12 stages IC2/IC3 patients nonoptimally staged, respectively (Fig. 3). In patients with stages IC2/IC3, no significant difference was observed in RFS or OS between patients optimally and patients nonoptimally staged (RFS: $P = 0.436$;

TABLE 3. The RFS and OS rates and RR of recurrent and death in patients with stages IA and IC1

Variable	Recurrence-Free Survival							Overall Survival			
	5-y	Univariate Analysis			Multivariate Analysis			5-y	Univariate Analysis		
No. Patients	Rate, %	Risk Ratio	95% CI	*P*	Risk Ratio	95% CI	*P*	Rate, %	Risk Ratio	95% CI	*P*
Age											
<50 y (n = 51)	88.1	1.313	0.393–4.447		1			91.4	1.188	0.260–5.461	
				0.652			0.898				0.821
≥50 y (n = 77)	92.9	1			1.108	0.325–3.602		96.0	1		
FIGO stage											
IA (n = 42)	97.6	1			1			97.6	1		
				0.071			0.058				0.262
IC1 (n = 86)	89.5	5.389	0.906–10.803		7.564	0.935–61.350		94.2	3.150	0.517–11.015	
Surgical staging category											
Optimal (n = 56)	98.2	1			1			100			
				0.021			0.033				0.024
Nonoptimal (n = 72)	87.5	7.679	1.228–13.348		9.551	1.194–76.335		91.6			
Adjuvant chemotherapy											
Chemotherapy (n = 111)	92.7	1			1			95.4	1		
				0.649			0.8305				0.257
Observation (n = 17)	88.2	1.423	0.264–8.425		1.187	0.248–5.685		94.1	2.492	0.403–29.646	

CI, Confidence interval; FIGO, International Federation of Gynecology and Obstetrics

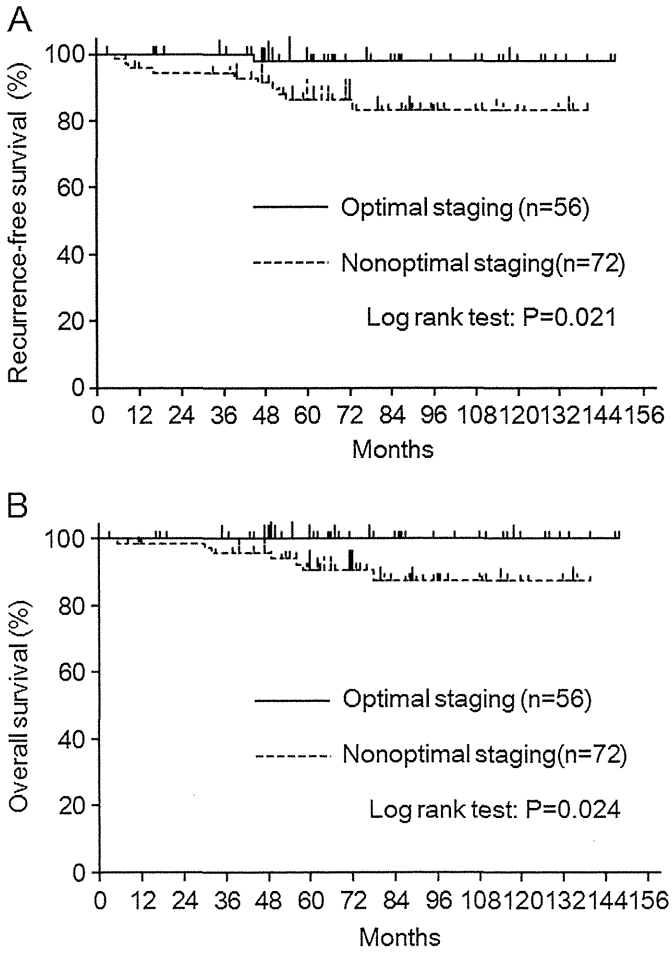

FIGURE 2. Kaplan-Meier curves for RFS (A) and OS (B) in patients with stages IA/IC1 by surgical staging category. Significant differences were observed in RFS and OS between patients optimally and nonoptimally staged (RFS: $P = 0.021$; OS: $P = 0.024$).

OS: $P = 0.238$; Fig. 3), patients younger than 50 years and 50 years or older (RFS: $P = 0.370$; OS: $P = 0.391$), patients with stage IC2 or IC3 (RFS: $P = 0.542$; OS: $P = 0.161$), or patients treated with TP or CPT-P (RFS: $P = 0.615$; OS: $P = 0.561$).

DISCUSSION

We retrospectively reviewed 165 stage I CCC patients consisting of 42 (25.5%) with stage IA, 86 (52.1%) with stage IC1, 13 (7.9%) with stage IC2, and 24 (14.5%) with stage IC3. The distribution of substage in our study was similar to several previous reports for Japanese patients with stage I CCC.[16,17] However, the incidence of stage IA (60.9%) in the Surveillance, Epidemiology and End Results Program data was higher than that in our report and previous reports for Japanese patients.[3,16,17] It has long been recognized that CCC is associated with endometriosis.[1] In keeping with the higher incidence of CCC in Asian women, some studies have reported higher prevalence rates of endometriosis in Asian women.[1] In fact, firm adhesion of tumor capsule to the retroperitoneum and/or the rectum due to endometriosis is commonly observed in Japanese patients with CCC. High incidence of IC1 (intraoperative capsule rupture) in our report and previous reports for Japanese patients was likely due to the adhesion.

Taxane and platinum adjuvant chemotherapy is recommended by several guidelines for stage I CCC patients disregarding the surgical staging category.[18,19] On the other hand, EORTC-ACTION demonstrated that completeness of surgical staging was an independent prognostic factor in early-stage EOC patients and that adjuvant chemotherapy in early-stage EOC was not effective after optimal surgical staging.[5] It was suggested that adjuvant chemotherapy in early-stage EOC was predominantly effective in patients with occult residual disease and that its effectiveness was dependent on the likelihood of remaining ovarian cancer spread.[5] In terms of lymph node assessment, the optimal staging defined in EORTC-ACTION included only lymph node sampling, but that did not include

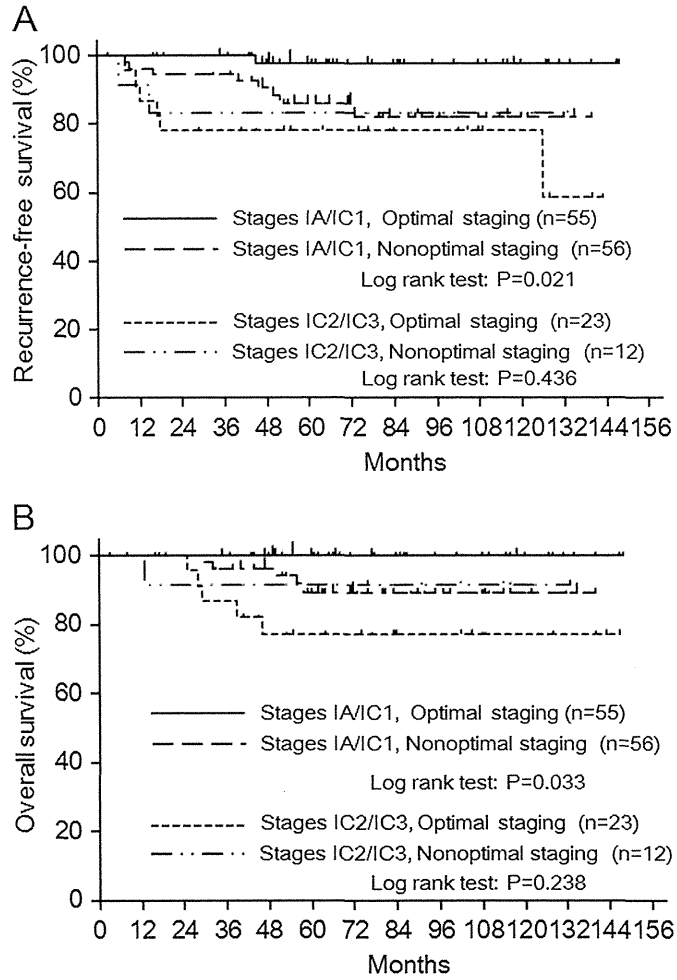

FIGURE 3. Kaplan-Meier curves for RFS and OS (B) in patients who received adjuvant chemotherapy by both stage and surgical staging category. Significant differences were observed in RFS and OS between stages IA/IC1 patients optimally and nonoptimally staged (RFS: $P = 0.021$; OS: $P = 0.033$), whereas no significant difference was observed in those between stages IC2/IC3 patients optimally and patients nonoptimally staged (RFS: $P = 0.436$; OS: $P = 0.238$).

systematic PEL-LNX and/or PAO-LNX. Takano et al[20] reported that the incidence of lymph node metastases in patients with clinical stage I CCC who underwent complete PEL-LNX and PAO-LNX was 7.5%. In this study, we detected lymph node metastases in 5 (5.9%) of 85 patients with clinical stage I CCC who underwent complete PEL-LNX and PAO-LNX (data not shown). In addition, first relapse was detected in the pelvic and/or para-aortic lymph nodes within 2 years in 4 nonoptimally staged patients, suggesting that they had occult residual disease in lymph nodes at presentation. Mahdi et al[21] reported that there was a trend toward an improved survival when more extensive LNX is performed in stage I CCC patients with histologically negative nodes (1-10 vs >10 nodes), although it did not reach statistical significance ($P = 0.064$). Conversely, Chan et al[22] demonstrated that LNX improved the survival in patients with non–clear cell EOC but not in those with CCC. To evaluate the impact of surgical staging in stage I CCC, we retrospectively reviewed outcomes in 165 stage I CCC patients who underwent optimal staging surgery including systematic PEL-LNX and PAO-LNX or nonoptimal staging surgery, but no significant difference was observed in RFS or OS (Table 2, Fig. 1). We also demonstrated that stages IA/IC1 was the only independent predictor of poor RFS and OS in stage I CCC but that surgical staging category was not (Table 2). Takano et al[20] retrospectively reviewed outcomes in both 124 CCC patients with pT1 pN0 M0 and 10 with pT1 pN1 M0 who underwent complete surgical staging procedures including PEL-LNX and PAO-LNX and 65 with pT1pNxM0 who were assessed for lymph nodes metastases by exploration or sampling. It was reported that peritoneal cytology status was the only independent prognostic factor for RFS but that completion of surgical staging procedures was not.[20] Higashi et al[17] reported that no significant difference was observed in RFS or OS of CCC patients between IA and IC1, but that CCC patients with IC2/IC3 showed a poorer RFS and OS than did those at IC1 and that the capsule status was an independent prognostic factor of a poor RFS and OS. Our results were similar to those previous reports.

In accordance with plans, we also assessed the impact of surgical staging, in stages IA/IC1 and stages IC2/IC3 separately. Significant differences were observed in PFS and OS between patients optimally and nonoptimally staged with stages IA/IC1, but no significant difference was found in those with stages IC2/IC3 (Table 3, Fig. 2). Moreover, we indicated for the first time that surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC (Table 3).

Because the patients were treated with adjuvant chemotherapy more frequently in the optimally staged group (97.5%) than in the nonoptimally staged group (80.0%), we performed a subset analysis in patients treated with adjuvant chemotherapy. Results in this subset analysis were similar in all patients. In a subset analysis, the 5-year RFS and OS rates in 55 patients optimally staged with stages IA/IC1 in the adjuvant chemotherapy group were 97.8% and 100%, respectively, and survival was longer than that of 56 stages IA/IC1patients nonoptimally staged (Fig. 3). We indicated that surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC patients treated with adjuvant chemotherapy. On the other hand, we cannot compare the outcome associated with adjuvant chemotherapy in each group because of small sample size of the observation group, although no significant difference was observed in RFS or OS by adjuvant chemotherapy and that was not an independent prognostic factor in stage I CCC. Mizuno et al[16] reported that the 5-year RFS rates in CCC patients who received comprehensive surgical staging and were treated with/without adjuvant chemotherapy were 93.8% (n = 16) and 100% (n = 25) for stage IA, and 86.6% (n = 75) and 94.1% (n = 18) for stage IC1, respectively, and concluded the routine adjuvant chemotherapy after comprehensive surgical staging may be unnecessary for patients with at least stage IA. Takada et al[23] reported outcome of stage I CCC patients who received comprehensive surgical staging consisting of 4 with stage IA and 11 with stage IC1 who received adjuvant chemotherapy and 16 with stage IA and 16 with stage IC1 who received no additional therapy. It was reported that no recurrence was observed in stage IA patients and that the 5-year RFS and OS rates in stage IC1 patients were 87.5% and 100% in the adjuvant chemotherapy group and 74.0% and 76.4% in the observation group, respectively, and suggested that postoperative adjuvant chemotherapy is not necessary for stage IA CCC patients but that adjuvant chemotherapy suppressed recurrence for stage IC CCC. Our results and previous reports show that the outcome in patients with stages IA/IC1 who received optimal surgical staging and adjuvant chemotherapy is favorable. However, survival benefit of adjuvant chemotherapy in patients with stages IA/IC1, especially in those with stage IC1, is controversial. At present, the Japanese Gynecologic Oncology Group (JGOG) is performing a randomized phase III trial of the necessity of adjuvant chemotherapy in stage I (stage IA/IB with grade2/3 or CCC, stage IC1) EOC after comprehensive staging surgery (JGOG3020, UMIN000008481), and the results are eagerly awaited.

No survival benefit from optimal staging surgery including systematic PEL-LNX and PAO-LNX was found in stages IC2/IC3 patients who received adjuvant chemotherapy in the present study (Fig. 3). These results suggest the existence of intra-abdominal microdissemination, which includes chemoresistant clones in these patients. We could not assess the survival benefit of adjuvant chemotherapy for stages IC2/IC3 in this trial because of small sample size of the observation group. However, Takada et al[23] reported that the 5-year RFS and OS rates in stages IC2/IC3 patients were 69.6% and 75.0% in the adjuvant chemotherapy group and 34.6% and 70.0% in the observation group, respectively, suggesting that adjuvant chemotherapy suppressed recurrence in stages IC2/IC3. In this study, there was no significant difference in RFS and OS between stages IC2/IC3 patients treated with TP and CPT-P therapy as adjuvant chemotherapy. Takakura et al[24] reported a randomized phase II trial of paclitaxel and carboplatin (TC) therapy versus CPT-P therapy as first line chemotherapy for CCC (JGOG3014). No significant difference was observed in progression-free survival for patients with no residual disease between the 2 treatment groups.[24] Kajiyama et al[25] found no significant difference in RFS or OS between stages I/II CCC patients who received TC and various conventional cisplatin-based chemotherapies. So to improve the prognosis of these patients, effective new antineoplastic agents and molecularly targeted agents should be

evaluated in prospective clinical trials. Because more than 80% of CCCs show activation of the AKT-mTOR (mammalian target of papamycin) pathway, exploration of the potential benefit of mTOR inhibitors is of great interest.[26] At present, the Gynecologic Oncology Group is performing a phase II trial of temsirolimus in combination with TC followed by temsirolimus consolidation as first-line therapy in the treatment of stage III-IV CCC (GOG-0268, NCI-2011-02653).

In this retrospective study, the prognosis for women with stage 1A/IC1 CCC is very good. Furthermore, surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC. The necessity of adjuvant chemotherapy for CCC patients optimally staged with stages IA/IC1 should be verified by a prospective randomized trial.

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GYNECOLOGIC ONCOLOGY

Success rate and safety of tumor debulking with diaphragmatic surgery for advanced epithelial ovarian cancer and peritoneal cancer

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Abstract
Purpose In advanced epithelial ovarian and peritoneal cancer, residual tumor diameter correlates with prognosis; therefore, maximum debulking and optimal surgery (OS) for residual tumors <1 cm is warranted. Here, we clarified the efficacy of tumor debulking with diaphragmatic surgery (DS).
Methods In 45 patients with epithelial ovarian or peritoneal cancer who underwent DS (ten, full-thickness resection; 35, stripping) between January 2010 and December 2013 at two related institutions, we retrospectively evaluated OS safety and success by surgical duration, blood loss, complications, hospitalization stay, and residual tumor diameter and site.
Results Blood loss was 4,090.8 and 2,847.9 mL; surgical duration was 485.2 and 479.5 min; hospitalization stay was 21.7 and 24.8 days; and complications included intraoperative thoracotomy in 17 and 7 patients, unexpected thoracotomy in 11 and 3, chest drain insertion in one and three, and pleural effusion in 14 and 7, in the primary debulking surgery (PDS) and interval debulking surgery (IDS) groups, respectively. OS was successful in all patients with complete surgery (CS: no residual tumor) achieved in 16 (50.0 %) and 9 (69.2 %), residual tumor diameter < 5 mm in 11 (34.4 %) and 2 (15.4 %), and residual tumor diameter < 1 cm in 5 (15.6 %) and 2 (15.4 %) in the PDS and IDS groups, respectively.
Conclusions Tumor debulking surgery with DS resulted in controllable blood loss, and OS was successful in all patients without severe complications or postoperative treatment delay. Currently, OS is considered to have very few benefits over CS; thus, the success rate of CS rate should be improved while maintaining safety.

Keywords Ovarian cancer · Diaphragmatic surgery · Debulking surgery · Peritoneal cancer

Introduction

Ovarian cancer has few subjective symptoms. Consequently, at present, approximately 40–50 % of cases are detected in advanced stages (III/IV), which may be attributed to the difficulty in early detection and mass screening. As a result, of all gynecologic malignancies, ovarian cancer has the highest mortality. Although the advent of paclitaxel has improved therapeutic outcomes of ovarian cancer, the 5-year survival rate of advanced cases remains low (25–37 %) and typically require multimodal therapeutic combinations of surgery and chemotherapy.

The first-line treatment of ovarian cancer is surgery, which generally involves bilateral salpingo-oophorectomy, total hysterectomy, and omentectomy. Staging by laparotomy is required to determine disease stage and involves intraperitoneal cytodiagnosis, intraperitoneal biopsy, and radical dissection (biopsy) of the retroperitoneal (pelvic and para-aortic) lymph nodes.

The prognostic factors of ovarian cancer include staging, histologic type, and residual tumor diameter after primary debulking surgery (PDS). Residual tumor diameter is considered a particularly important factor. Surgery, such as resection of disseminated and metastatic lesions, is

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performed so that the margin of the residual tumor is as close to zero as possible. Tumor debulking surgery is generally performed as a first-line treatment, even in stage IV cases with distal metastasis, excluding those in which distal metastasis impacts short-term survival. Prognosis is improved when the residual tumor diameter is <1 cm, in which case surgery is referred to as optimal surgery (OS). Therefore, the standard treatment for advanced ovarian cancer at the time of primary surgery is maximum debulking surgery followed by chemotherapy. However, views on OS have changed in recent years. In 2009, Du Bois et al. [1] reported that other than reducing the size of the residual tumor, OS offers very few benefits to patients with advanced ovarian cancer (stage IIb or greater). In our facilities, we recently adopted diaphragmatic surgery (DS) as a part of OS. Nonetheless, we currently aim for complete surgery (CS) for cases of advanced ovarian cancer.

Patients and methods

In the present study, we examined 45 patients with epithelial ovarian cancer or peritoneal cancer who underwent tumor debulking with DS at two related institutions between January 2010 and December 2013. All patients underwent standard surgical procedures (bilateral salpingo-oophorectomy, total hysterectomy, or omentectomy) and retroperitoneal lymph node dissection (biopsy), in addition to DS (stripping and full-thickness resection). The procedure of diaphragmatic stripping conducted at our hospital is as follows. To ensure an adequate field of view, images of the state of liver mobilization (Fig. 1a) are obtained, after which, diaphragmatic stripping (Fig. 1b) is performed. At this point, the liver is fixed which requires approximately 10–15 min. Soon after fixation, blood flow is resumed and surgery is continued. In cases undergoing diaphragm full-thickness resection (Fig. 2), the diaphragm is reconstructed (Fig. 2, 3) using absorbable sutures (PDS in our hospital). Thereafter, deflation is performed using a narrow tube (Fig. 3) at our institution (20 G; BD Insyte Autoguard Shielded IV Catheter; Becton–Dickinson, Tokyo, Japan) and the chest is closed. Finally, a bubble test is performed under positive pressure ventilation to confirm sufficient airtight chest closure. Furthermore, for all patients, post-operative chest radiography is performed in the operating room to confirm the absence of pneumothorax.

Results

The subject cohort comprised 45 patients (mean age, 53 years), including 41 with ovarian cancer and four with peritoneal cancer. The histological types included serous adenocarcinoma ($n = 31$), endometrioid adenocarcinoma ($n = 4$), clear cell adenocarcinoma ($n = 6$), mixed-type ($n = 3$), and others ($n = 1$). With respect to staging, two patients had stage IIIb disease, 33 had stage IIIc, and 10 had stage IV. With respect to the type of surgery, PDS was performed in 32 cases and interval debulking surgery (IDS) in 13 (Table 1). In the PDS and IDS groups, the mean blood loss volume was 4,090.8 and 2,847.9 mL, and the mean surgical duration was 485.2 and 479.5 min, respectively. Stripping was performed in 26 and 9 patients, and full-thickness resection was performed in six and four patients, respectively. Complications included intraoperative thoracotomy in 17 and 7, unexpected thoracotomy in 11 and 3, chest drain insertion in one and three, and postoperative pleural effusion in 14 and 7 patients, respectively. The mean length of hospitalization was 21.7 and 24.8 days, respectively. OS was successfully completed in all patients. In the PDS and IDS groups, CS was achieved (CS: no residual tumor) in 16 (50 %) and 9 (69.2 %) patients, and the residual tumor diameter was<5 mm in 11 (34.4 %) and 2 (15.4 %) patients and

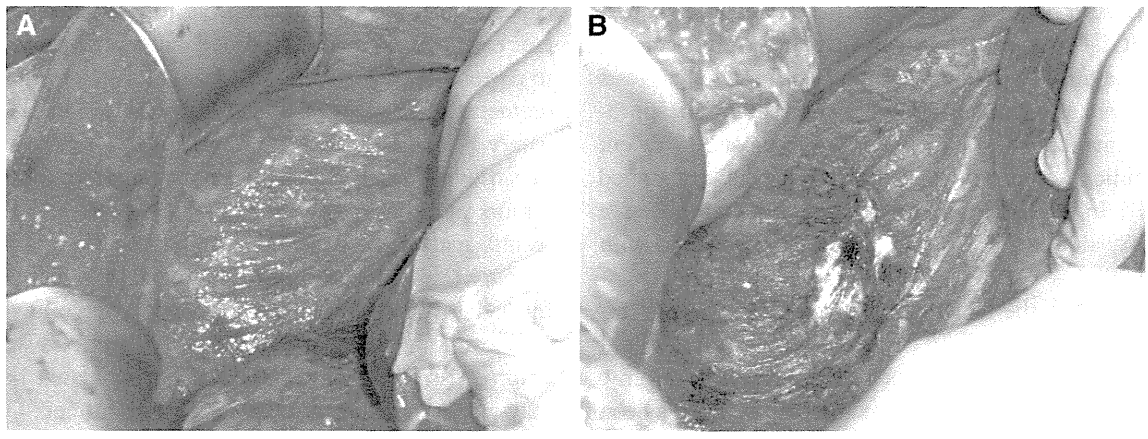

Fig. 1 **a** Diaphragm disease. **b** Diaphragmatic stripping is performed