the use of postoperative CCRT against SCCC has become widely accepted.

In this study we analyzed a series of 9 patients with SCCC. Of them, five patients received surgery followed by CCRT using the VAC/PE regimen. Notably, all five patients with early stage SCCC including two cases with bulky tumors had no pelvic recurrence, a median survival of 47.4 months and an OS rate at five years of 80%. Although limited by the small number of patients included in this analysis, we did show improvement in the overall survival rate over the previously reported five-year survival of 31.6-46.6% for stage I-IIA patients (Chan et al. 2003; Lee et al. 2008; Cohen et al. 2010). In addition, Cohen et al. reported that radical hysterectomy was an independent prognostic factor for survival in a multivariate analysis of 188 patients with SCCC (Cohen et al. 2010). These results suggest that CCRT using the VAC/PE regimen in addition to surgical resection may improve both local control and survival in patients with early stage disease.

We applied the combination VAC/PE regimen with radiation to the patients with advanced stage disease, with post-treatment hysterectomy reserved for those patients with partial responses. While one patient (patient #2) with advanced disease entered long term remission following an interval hysterectomy, two patients treated with hysterectomy after CCRT died of their disease (patient #2, 3). These results suggest that hysterectomy after CCRT may confer little benefit in the setting of advanced stage SCCC; although some studies report that extrafascial hysterectomy after CCRT is a reasonable option if there are histological factors suggesting poor prognosis (Motton et al. 2010).

Hoskins et al. reported that stage III/IV patients with SCCC had a 38% three-year recurrence-free survival if treated with combination chemotherapy (PE) in addition to concurrent radiation (Hoskins et al. 2003). We experienced two stage IVB patients treated with CCRT using the VAC/PE regimen, one of whom (patient #1) had prolonged survival without recurrence. When radiotherapy and chemotherapy are given together, the evaluation of toxicities becomes important. We adopted the VAC/PE regimen instead of the PE regimen, with a similar toxicity profile to that reported by Hoskins et al. There were no treatment-related deaths in either protocol. Although there are no randomized trials comparing chemotherapy alone versus CCRT, either as a primary therapy, or in the adjuvant setting following radical hysterectomy, CCRT using the VAC/PE regimen is feasible and has the potential to cure some SCCC patients with metastatic disease.

Limitations of this study include its small size and that all patients were treated at a single institute. A strength, however, is that the treatment strategies (radical hysterectomy with adjuvant CCRT using VAC/PE regimen for early stage patients, and definitive radiation therapy with VAC/PE chemotherapy for advanced stage patients) were uniform across the study period. In conclusion, combination chemotherapy (VAC/PE) in addition to concurrent radiation is feasible in both the primary and adjuvant settings. Postoperative adjuvant CCRT using the VAC/PE regimen may improve both local control and prognosis for patients with early stage disease. Given the rarity of SCCC, multi-institutional clinical trials are required to attain sufficient power to develop standardized treatment protocols.

Conflict of Interest

The authors report no conflict interest.

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Tako-Tsubo Cardiomyopathy Caused Immediately following Cesarean Section Delivery of Triplets: A Case Report

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Established Facts

- Tako-tsubo (TT) cardiomyopathy is caused by emotional or physical stress.
- TT cardiomyopathy is characterized by transient left ventricular dysfunction with chest symptoms and electrocardiographic changes that mimic those of acute myocardial infarction in patients with normal findings on coronary angiography.
- There have been a limited number of case reports of TT cardiomyopathy, especially related to pregnant women, which is very rare indeed.

Novel Insights

- We experienced the patient diagnosed as TT cardiomyopathy which merged for the pregnancy.
- It was thought that TT cardiomyopathy resulted due to the combination of several factors, including long-term bed rest, ritodrine hydrochloride treatment and cesarean section.
- The patient was healed by appropriate treatment.

Key Words
Tako-tsubo cardiomyopathy · Triplets · Ritodrine hydrochloride · Cesarean section

Abstract
The name 'tako-tsubo' cardiomyopathy was initially used to describe a unique 'short-neck round-flask'-shaped form of left ventricular apical ballooning, resembling a Japanese tako-tsubo, a jar (tsubo) used for capturing octopus (tako). Tako-tsubo cardiomyopathy exhibits acute onset, transient left ventricular apical wall motion abnormalities with chest symptoms and minimal myocardial enzymatic release, mimicking acute myocardial infarction in patients without angiographic stenosis on coronary angiography. There have been few case reports on tako-tsubo cardiomyopathy, and this disorder is especially rare in pregnant women. A 30-year-old woman who was pregnant with triplets, and had been treated with ritodrine hydrochloride for 12 weeks for threatened premature delivery, underwent cesarean

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section with spinal anesthesia at 30 weeks' gestation. Three hours later, she complained of acute chest pain, dyspnea and episodes of unconsciousness. She was transferred to the intensive care unit and intubated for ventilatory support. We diagnosed heart failure due to tako-tsubo cardiomyopathy based on heart ultrasonography, blood tests, chest X-ray, electrocardiogram and myocardial scintigraphy. She was extubated from the ventilator after 3 days of catecholamine, furosemide and carperitide administration. She was discharged from the hospital on day 53 without symptoms.

Introduction

Tako-tsubo (TT) cardiomyopathy, also known as TT syndrome or transient left ventricular (LV) apical ballooning, is characterized by reversible LV dysfunction which cannot be explained based on significant coronary artery disease [1]. In Japan, there have been a limited number of case reports on TT cardiomyopathy but very few on pregnant women as this condition is quite rare during pregnancy. We report an extremely rare case of TT cardiomyopathy with symptoms similar to those of acute myocardial infarction, diagnosed as heart failure. The patient was pregnant with triplets and underwent elective cesarean section.

Case Report

A 30-year-old healthy woman was admitted at week 11 of a triplet gestation with threatened abortion, as indicated by vaginal bleeding and lower abdominal pain necessitating hospitalization. The patient had no family history of heart disease.

History of gravidity and parturition: gravitas 2, para 0 (1st: extrauterine pregnancy at 27 years of age; 2nd: stillbirth suspected to be due to Potter syndrome at 29 years).

The patient was admitted to our hospital for bed rest for 18 weeks, and was treated with intravenous isoxsuprine hydrochloride. At 18 weeks' gestation, we considered a medication change to be necessary based on marked symptom exacerbation without premature rupture of membranes (PROM). Therefore, ritodrine hydrochloride was administered in increasing doses (50–200 μg/min) starting at 25 weeks' gestation. In addition, to prevent PROM and preterm delivery, the cerclage procedure was performed uneventfully with spinal anesthesia at 25 weeks' gestation. At 30 weeks' gestation, the patient underwent cesarean section under secondary spinal anesthesia. The operation time was 50 min, and intraoperative blood loss volume was 1,199 g. During the postoperative period, urine volume decreased after 1 h, and she developed sudden dyspnea and difficulty breathing 5 h later. The patient was transferred to the intensive care unit, and was intubated for respiratory support, because SpO_2 dropped to 70% and a gradual deterioration of consciousness was observed.

Table 1. Results of blood test: first time in the intensive care unit

WBC, μl	14.0×10^3
RBC, μl	369×10^4
Hb, g/dl	12.0
Ht, %	37.9
Plt, μl	100×10^3
TP, g/dl	4.8
Na, mEq/l	138
K, mEq/l	5.4
Cl, mEq/l	110
UN, mg/dl	22.7
CRE, mg/dl	1.1
UA, mg/dl	8.2
GOT, IU/l	54
GPT, IU/l	18
LDH, IU/l	956
T-Bil, mg/dl	1.1
CK, IU/l	1,703
CK-MB, IU/l	60
CRP, mg/dl	0.3
pH	7.191
PCO_2, mm Hg	46.5
PO_2, mm Hg	53.8
BE, mmol/l	–10.5
SpO_2, %	80.0
APTT, s	33.7
PT, s	12.5
Fbg, mg/dl	106.5
AT-III, %	70
FDP, μg/ml	79
D-Dimer, μg/ml	20.5
Troponin T	negative
Adrenaline, pg/ml	>5
Noradrenaline, pg/ml	175
Dopamine, pg/ml	50,357

Table 1 presents the blood examination findings. CPK (1,703 IU/l) was elevated at the onset. CTR expanded to 57% (fig. 1a). Electrocardiograms (ECG) indicated ST elevation in aVR and aVL, and a negative T wave in I-III, aVF, and V2–V6 on 12-lead ECG (fig. 1b). Continuous ECG monitoring and degradation of broad products with exercise indicated LV pathology. The LV ejection fraction (27%) and medium-grade pericardial effusion were observed on an echocardiogram (ECHO). LV dysfunction typical of TT cardiomyopathy was evident on ECHO (fig. 2a, b). We also employed color Doppler-ECHO, but no stenosis of the descensus rami of the left anterior coronary artery was detected (fig. 2c). Furthermore, cardiac muscle scintigraphy showed no ischemic changes (fig. 3). We treated the patient with dopamine hydrochloride, dobutamine hydrochloride, furosemide and carperitide in the intensive care unit. The oliguria resolved satisfac-

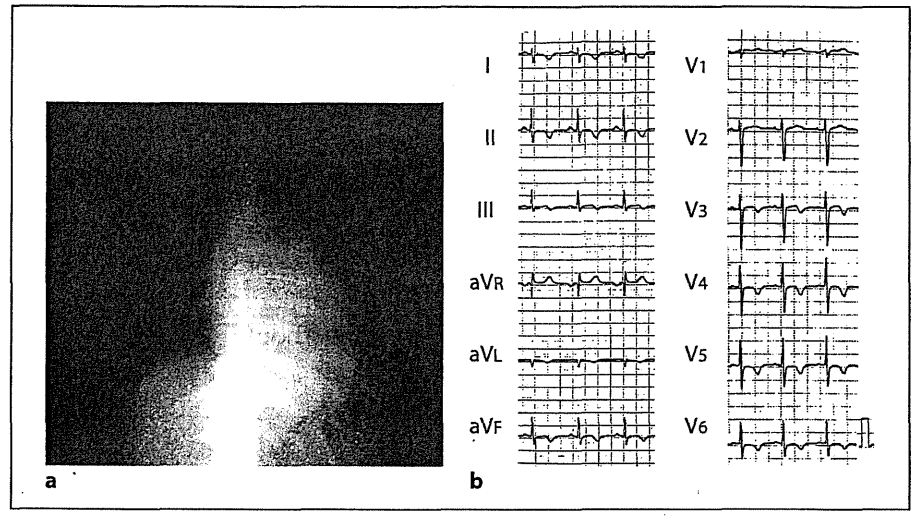

Fig. 1. a Pulmonary congestion (CTR: 57%) was imaged in chest X-ray. **b** ST elevation in aVR and aVL, and negative T waves in I–III, aVF, V2–V6.

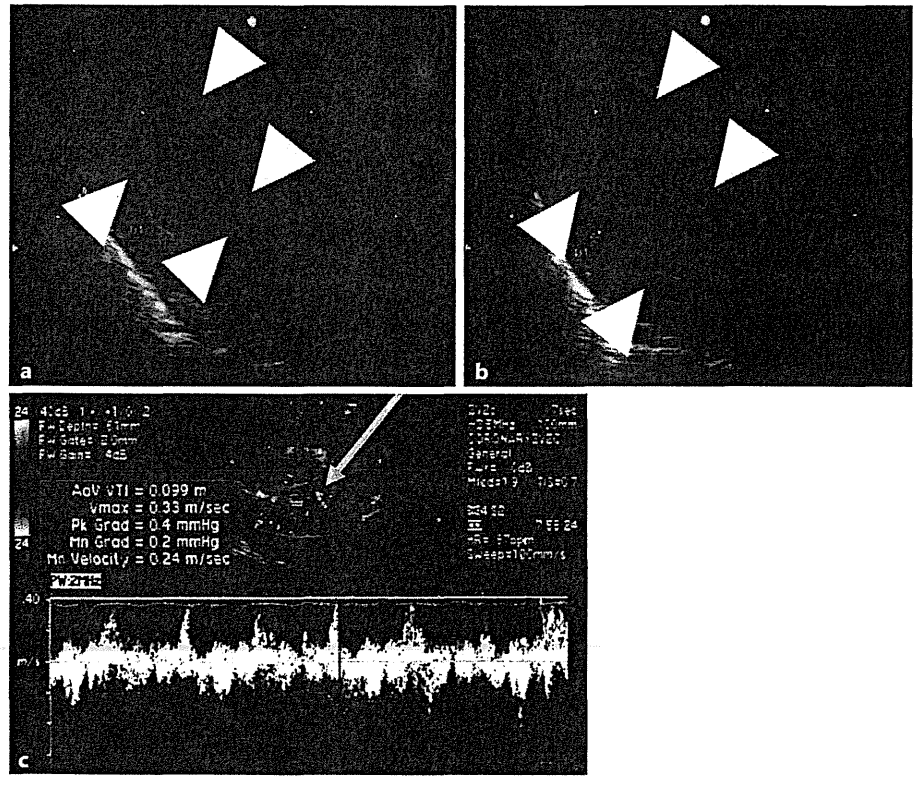

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Fig. 2. a, b Apical ballooning and hyperkinesis of the base were observed. **c** High-speed blood flow was not recognized in the descensus rami of the left anterior artery (arrow).

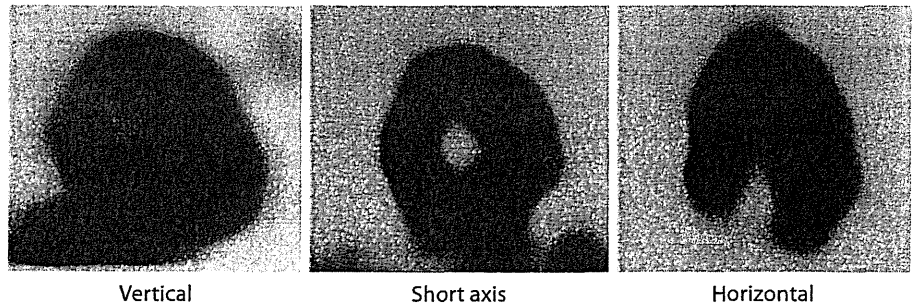

Fig. 3. ^{99m}Tc-tetrofosmin cardiac muscle scintigram: a perfusion defect of the myocardium was not recognized.

torily resulting in reduced pulmonary congestion according to the anterior-posterior chest X-ray, and she was extubated from the ventilator 3 days later. ECHO confirmed an ejection fraction of 62% with no wall motion abnormalities, and heart failure symptoms steadily resolved up to day 53. The final outcome was good.

Discussion

TT cardiomyopathy was first described by Kuramoto et al. [2]. TT cardiomyopathy is characterized by transient LV dysfunction with chest symptoms and ECG changes that mimic those of acute myocardial infarction in patients with normal findings on coronary angiography [3]. TT cardiomyopathy alone has not yet been explained, and it is speculated to be induced by emotional or physical stress [4]. Several general observations have been made in Japan [5–10]. D'Amato et al. [11] reported pregnant woman with TT cardiomyopathy who did not exhibit coronary artery disease. However, she did have severe impairment of cardiac function with typical ECHO and ECG findings.

Gologorsky and Gologorsky [12] reported the utility of transesophageal ECHO images of intraoperative TT cardiomyopathy in a female patient under general anesthesia, and stress cardiomyopathy was suspected in this case based on computed tomographic angiography and catheterization. However, Gologorsky and Gologorsky [12] concluded that transesophageal ECHO was useful in the differential diagnosis of intraoperative hypotension and suspected acute coronary syndrome. We consider coronary angiography to be an efficient examination for making an accurate diagnosis, for example when distinguishing among TT cardiomyopathy, apical ballooning syndrome and stress cardiomyopathy. We determined that our present patient, who was pregnant with triplets and receiving tocolysis therapy, had a serious condition. We thus decided to diagnose this patient based on ECG findings. Therefore, coronary angiography was not performed. We excluded coronary artery diseases by performing coronary artery color-Doppler ECHO and myocardial scintigraphy, which are less invasive procedures. Consales et al. [13] reported a relationship between TT cardiomyopathy and general anesthesia, arguing that, during general anesthesia and particularly at induction, imperfect control of catecholamine excess may induce cardiac damage in predisposed subjects. Furthermore, Crimi et al. [14] reported that acute, reversible, stress-induced cardiomyopathy (SIC) was associated with cesarean delivery under spinal anesthesia, suggesting that the occurrence of SIC in this population may be more frequent than thought, and that a link may exist between SIC and subclinical peripartum cardiomyopathy. We believe that the TT cardiomyopathy in our present patient with a triplet gestation was related to the stress of ritodrine hydrochloride treatment to prevent from PROM. In 1988, Blickstein et al. [15] reported that pulmonary edema was induced by an increase in the dose of ritodrine hydrochloride in a patient receiving this drug for 28 days for preterm contractions. After initial therapy, cardiologic evaluation revealed peripartum cardiomyopathy. In addition, Lampert et al. [16] reported that gravitas undergoing long-term β-sympathomimetic tocolysis experienced close evolution of cardiac function. Citro et al. [17] reported the TT cardiomyopathy occurred after ergonovine injection. However, in this case, only oxytocin injection was used to prevent atonic bleeding of the uterus after cesarean section during the early postpartum period. Therefore, the ergonovine was not related to TT cardiomyopathy.

We consider ritodrine hydrochloride to increase heart rate and increase the circulating blood volume into the right ventricle, ultimately triggering pulmonary hypertension and edema with the increased volume of blood flow into the lung, resulting in LV dysfunction. Therefore, we speculate that our case developed cardiomyopathy via this mechanism. In addition, absence of coronary artery disease in a healthy woman pregnant with triplets, which would limit lung volume for breathing, in combination with several factors, including long-term bed rest, ritodrine hydrochloride treatment and cesarean section, would predispose to TT cardiomyopathy. In this case, we can rule out acute myocardial infarction based on the findings of coronary artery color Doppler and cardiac muscle scintigraphy, though she did have an abnormally high CPK value and the T-wave was negative. The treatment indicated general cardiac insufficiency, and she recovered from the emergent condition. The patient's general condition was so poor that we chose a less invasive procedure as the first diagnostic option. Dopamine was used to maintain blood pressure, dobutamine to increase cardiac contractility. Both of these treatments were effective in this case, though we had also considered the option of intra-aortic balloon pumping in the event of lack of a satisfactory therapeutic effect. In multiple pregnancy cases, we advocate close clinical observation of cardiac function, because these pregnancies necessitate prolonged bed rest and tocolysis.

Conclusion

We have described herein our clinical experience with complete recovery from TT cardiomyopathy associated with three significant factors, i.e. triplet gestation, ritodrine hydrochloride therapy and cesarean section.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Original Article

Histological Grading of Ovarian Clear Cell Adenocarcinoma: Proposal for a Simple and Reproducible Grouping System Based on Tumor Growth Architecture

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Summary: In this study, we aimed to develop a histological grading system for ovarian clear cell adenocarcinoma (CCA), based on the tumor growth architectures. Cases were defined as Group A if ≥90% of a tumor examined was composed of well-differentiated tubulocystic and/or papillary architectures; Group C if at least 10% of the tumor was composed of very poorly differentiated histology (i.e. solid masses or individual infiltrating tumor cells with no or little glandular/papillary differentiation); and tumors not corresponding to the first 2 descriptions were defined as Group B. The interobserver reproducibility and prognostic value of the assigned groups were analyzed for 159 CCAs from 5 institutions. The level of agreement in assigning the groups between 2 pathologists was 88.7% ($\kappa = 0.82$). After consensus was reached, 46 (29%), 79 (50%), and 34 (21%) tumors were classified in Groups A, B, and C, respectively. In early-stage cases [International Federation of Gynecology and Obstetrics (FIGO) stage I–II], Group A tumors had significantly better outcomes (100% 5-yr survival) than Group B tumors (82% 5-yr survival, $P = 0.024$ by log-rank test) or Group C tumors (56% 5-yr survival, $P = 0.00054$ by log-rank test). Moreover, early-stage Group B tumors had significantly better outcomes than Group C tumors ($P < 0.001$ by a generalized Wilcoxon test). In advanced cases (FIGO stage III–IV), Group A tumors had significantly better outcomes than Group C tumors (52% vs. 16% 5-yr survival, respectively, $P = 0.043$)..Group A and C tumors defined with our system were identified to have favorable and unfavorable prognostic factors, respectively, independent of the clinical stage of the disease and presence of residual tumors after the initial surgery. The

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proposed grouping system could divide patients with CCA into 3 subgroups with distinct prognostic indications, providing a 3-tier histological grading system for ovarian CCA. **Key Words:** Ovarian cancer—Clear cell adenocarcinoma—Histology—Tumor differentiation—Histological grade.

Clear cell adenocarcinoma (CCA) has been recognized as a highly lethal histological subtype of ovarian epithelial malignancies (1–9). Although the poor prognosis of ovarian CCA is thought to result primarily from its highly chemoresistant nature, some studies have reported aggressive behavior even at an early stage (10–13).

It is a generally accepted idea that the histological grade or degree of tumor differentiation is of prognostic value in human epithelial malignancies, but neither the histological features predictive of clinical outcome in patients with CCA nor grading methods for this carcinoma have been established yet (1,4). A probable reason is the considerable histological variation in CCA as compared with other histological subtypes of ovarian carcinomas (i.e. serous, endometrioid, or mucinous histology), and the majority of cases consist of at least 2 of the main 3 architectural features, including tubular (cystic), papillary, or solid patterns. Moreover, the percentage of each growth pattern differs between sections from different blocks within the same tumor. Therefore, the measurement of the extent of tumor differentiation or histological grading of ovarian CCA is often perplexing, especially when the architectural grade is determined by the ratio of glandular or papillary patterns to the solid growth pattern, that is, in the FIGO grading system (14), or when the prominent architectural pattern is determined, that is, with the Shimizu-Silverberg grading system (15).

We have previously reported that the presence of poorly differentiated histological features of CCA (i.e. tumor cells showing solid-sheet, cord, or diffuse infiltrative architectures with no or small extent of glandular formation) could significantly predict the clinical outcome of the patients (16). These findings led us to hypothesize that the least differentiated tumor components in a tumor, even those that are not a prominent histological feature, determine the clinical behavior of ovarian CCA. Moreover, if the histologically well-differentiated parts of the CCA were identified, tumors consisting mostly of such histology would constitute a relatively favorable prognostic subgroup of ovarian CCA. A more comprehensive histological grading system could be developed when these hypotheses are validated in a number of CCA cases.

In this study, assuming that well-constructed tubulo-cystic or papillary architecture in CCA could be regarded as a form of relatively well-differentiated histology of this carcinoma type, we aimed to develop a 3-tier histological grading system, which is more complete than the previously reported binary classification for ovarian CCA (16). The cases were divided into 3 subgroups based on the histological tumor growth architectures within a tumor. We grouped 159 cases of pure-type ovarian CCA with this system and analyzed its prognostic performance with respect to interobserver reproducibility.

MATERIALS AND METHODS

Cases Enrolled

This study was performed with approval from the Institutional Review Board on ethical issues of the National Defense Medical College, Japan. Between 1988 and 2004, 159 patients with pure-type CCA were identified by scanning the medical records of the collaborating institutions belonging to the Japan Clear Cell Carcinoma Study Group: the National Defense Medical College Hospital (n = 82), Aichi Cancer Center Hospital (n = 29), Osaka City General Hospital (n = 25), Yamagata University Hospital (n = 13), and Tottori University Hospital (n = 10). These cases were the same as those enrolled in an earlier series (16), and the characteristics of the study population are summarized in Table 1.

Clinicopathological details such as patient age, clinical stage of the disease, residual tumors after initial cytoreductive surgery, and overall survival were assessed for all patients. All 159 patients underwent initial surgical cytoreduction, that is, salpingo-oophorectomy, hysterectomy with or without peritoneal omentectomy, pelvic lymphadenectomy, and para-aortic lymphadenectomy. None of the patients had undergone neoadjuvant chemotherapy or radiation therapy before the initial surgery. One hundred and fifty patients (94%) received

TABLE 1. *Clinical characteristics of the enrolled patients*

Parameters	No. cases (%)
Age, year [median (SD)]	53.2 (8.3)
FIGO stage	
I	85 (53)
Ia	23 (14)
Ic	62 (39)
II	22 (14)
III	46 (29)
IV	6 (4)
Diameter of residual tumor	
0 cm	117 (74)
<1 cm	19 (12)
≥1 cm	23 (14)
Response to first-line chemotherapies	
CR/PR	12 (34)
SD/PD	23 (66)

CR, indicates complete response; FIGO, International Federation of Gynecology and Obstetrics; PD, progressive disease; PR, partial response; SD, stable disease.

postoperative platinum-based chemotherapies after the initial surgery. A second-look operation or second reductive surgery was carried out based on surgeon's preference.

Clinical response to chemotherapy was evaluated with computed tomography or magnetic resonance imaging and assessed for 35 patients with measurable residual tumors after initial surgery. A complete response (CR) was defined as the disappearance of all detectable disease for at least 4 weeks; a partial response (PR) was a greater than 50% decrease in tumor size for at least 4 weeks; and stable disease (SD) was the absence of any significant change in measurable lesions for at least 4 weeks (between a decrease of <50% and an increase of <25%). Progressive disease (PD) was defined as the appearance of a new lesion or a greater than 25% increase in tumor size. Of the 35 patients, 12 (34%) showed an effective response to chemotherapy (CR or PR), and 23 (66%) were defined as SD or PD.

The average follow-up period after the initial surgery was 47.4 months, ranging between 1 and 182 months. Survival duration was determined as the time from the date of primary surgery until death or the date of last follow-up. Of the 159 patients, 45 (28.3%) died due to the tumor burden.

Histological Grouping Method

All specimens were formalin-fixed and paraffin-embedded; 4-μm-thick sections were prepared for hematoxylin and eosin staining. For each case, all histological slides of the primary tumor were screened at the respective collaborating institution, and at least 3 slides suitable for histological examination and grading of the primary CCA were selected. These selected slides were independently reviewed for histological assignment by 2 pathologists (S.Y. and H.S.) without knowledge of the patient's clinical course. The group for an individual tumor was determined as follows:

Group A

Tumors were defined as Group A if a tumor showed, entirely or mostly (≥90%), well-differentiated (or well-constructed) tubulocystic and/or typical papillary growth architectures of CCA (Fig. 1), and the percentage of the less-differentiated histological components described in the sections for Group B or C accounted for less than 10% of the tumor area. In short, the well-differentiated tubulocystic growth architectures were defined as the presence of either 1 or a combination of the following structures: (1) a microcystic architecture composed of large, closely packed, uniformly cystic, proliferating tumor cells, usually intervened by thin stroma (Fig. 1A); or (2) a uniform tubular architecture composed of medium-sized and uniformly rounded glands delineated by tumor cells (Fig. 1B). The papillary growth was defined as well-differentiated or typical when the papillary structure was uniform and did not contain solid-appearing growths, whereas the growth was defined as nontypical when the papillary architecture was judged as solid-appearing growths by fusiform papillae.

Group B

Tumors were defined as Group B if tubular and/or papillary growth other than well-differentiated growth architectures were present in more than 10% of the tumors examined (Fig. 2), and the percentage of the very poorly differentiated histological components described in the sections for Group C accounted for less than 10% of the tumor area. The tubular and papillary architectures other than well-differentiated growths were represented as follows: (1) solid-appearing growth with fusiform glandular or papillary architecture (Figs. 2A, B); and (2) infiltrative small tubular pattern characterized by variously shaped, small glands of tumor cells (Fig. 2C). To define a tumor growth feature as the stated solid appearing, and to exclude the very poorly differentiated architectures, 2 or more easily discernible glandular spaces in a low-power field (5.51 mm^2 using 10× objective lens) were required (Fig. 2D).

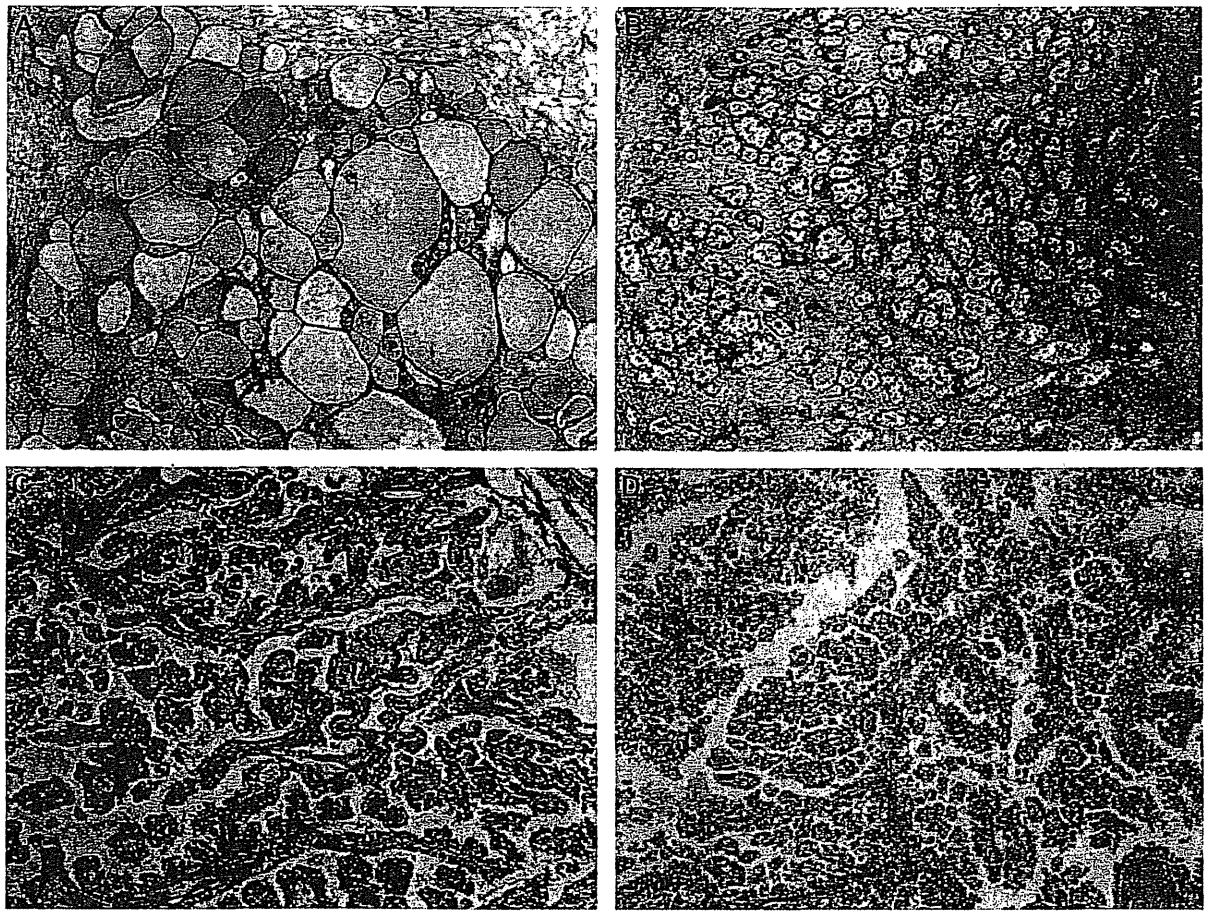

FIG. 1. Representative features of well-differentiated histology of clear cell adenocarcinoma. (A) Microcystic pattern. (B) Uniform tubular pattern. (C) and (D) Typical papillary pattern. Hematoxylin and eosin staining, original magnification 40 × for (A) and (B) and 100 × for (C) and (D).

Group C

Tumors were defined as Group C if very poorly differentiated components were present in more than 10% of the tumors examined. Very poorly differentiated features were defined as follows: solid sheet-like tumor cell growth, or cord or diffuse infiltrative architecture with little or no glandular spaces (Fig. 3). Small foci of glandular formation by tumor cells with their long axis perpendicular to the lumen may be discerned, but should not exceed 1 distinct glandular space in a low-power field (5.51 mm^2 using 10 × objective lens). Cytoplasmic lumina, vacuole-like spaces in tumor cell cytoplasm, and microcystic degeneration in the solid sheet-like growth of tumor cells were not considered glandular formation.

Although the histological grading was performed using low-power microscopic examination as a rule (4 × or 10 × objective lens), high-power examination (usually 20 × objective lens) was used where appropriate, especially when distinguishing true glandular spaces from pseudolumina in the solid architecture of tumor growth. The growth architecture of putative precursor lesions for ovarian CCA, namely endometriotic cysts and clear cell adenofibromatous components adjacent to CCAs, was not evaluated for the assignment. In addition, tumor cell types (i.e. clear cell, hobnail, signet ring, or tumor cells with abundant eosinophilic cytoplasm), presence or absence of necrosis, stromal hyalinization or myxoid changes, hemorrhage, calcification, and stromal inflammatory infiltrates were not considered for the histological assessment used in this study. When the 2 observers disagreed over the assignment of a group, the cases were discussed and a multiheaded microscope was used to achieve a consensus.

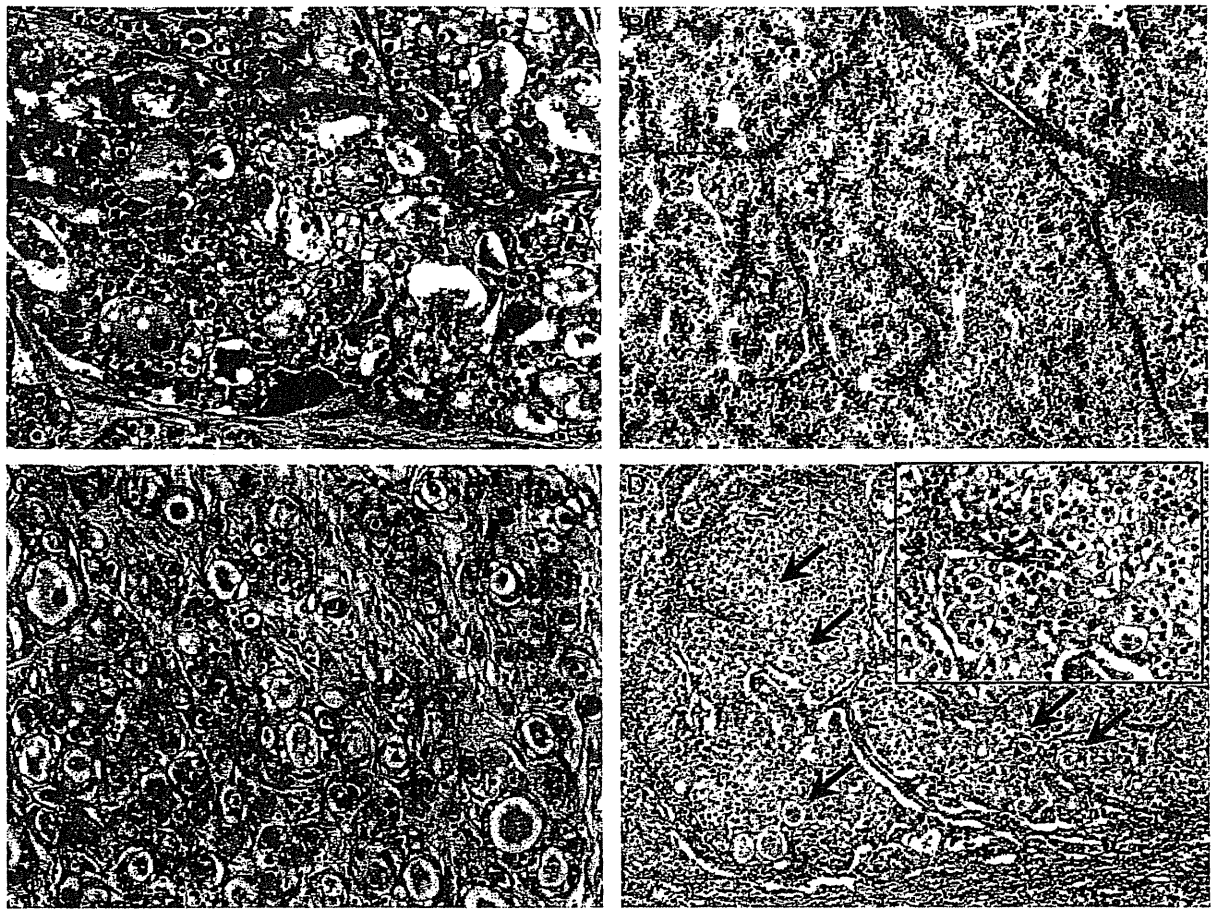

FIG. 2. Representative features of tubular and/or papillary growth of clear cell adenocarcinoma (CCA) other than well-differentiated tumor growth architectures. (A) Fusiform tubular pattern forming the so-called cribriform architecture. (B) Solid-appearing growth along with fusiform papillae. The fibrovascular connective tissue cores of the papillae are easily visualized. (C) CCA histology with the infiltrative small tubular pattern consists of small, variously shaped, infiltrative glands of tumor cells. (D) Solid-appearing growth with easily discernible glandular spaces (arrows). Inset indicates the glands surrounded by tumor cells that have long axes arranged perpendicular to the lumen. Hematoxylin and eosin staining, original magnification 100 × for (D) and (B) and 200 × for (A), (C) and the inset in (D).

Statistical Analyses

Statistical analyses were performed using StatMate III software (ATMS, Tokyo, Japan). Comparisons between parameters were computed with the χ^2 test. For survival analysis, Kaplan-Meier curves were drawn, and differences between the curves were calculated with the log-rank and generalized Wilcoxon tests. Tumors from various subgroups were stratified into 2 groups for analysis: FIGO stage I to II (early stages) and FIGO stage III to IV (advanced stages). The Cox proportional hazard general linear model computed independent prognostic significance. A difference of $P<0.05$ was considered statistically significant.

Kappa statistics and percentage of agreement were applied to test the reproducibility of the proposed grouping method between the observers. As a measurement of agreement, a kappa coefficient was interpreted as follows: 0.00 to 0.20, poor; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and 0.80 to 1.00, almost perfect.

RESULTS

Interobserver Reproducibility of the Proposed CCA Grouping System

The reproducibility of histopathological assessment of this series is presented in Table 2. The level of agreement was almost perfect (88.7% agreement, $\kappa = 0.82$).

Distribution of the Groupings, Their Relationship to Clinical Stage, and Response to Chemotherapy

After a consensus for the grouping of each case was achieved using the proposed grouping system, 46

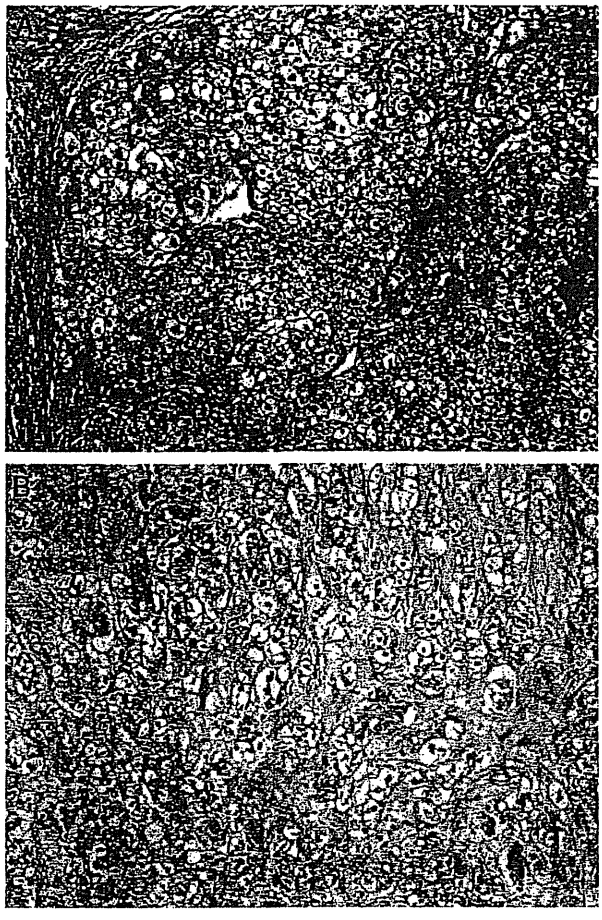

FIG. 3. Representative features of very poorly differentiated histological features of clear cell adenocarcinoma. (A) Solid sheet-like growth of tumor cells without distinct glandular spaces. (B) Diffuse infiltrative growth of small clusters or individual tumor cells. Hematoxylin and eosin staining, original magnification 100 × for (A) and (B).

(29%), 79 (50%), and 34 (21%) cases were classified as Group A, B, and C, respectively (Table 2).

There was no correlation between the histological grouping and clinical stage of the disease (Table 3). In contrast, a measurable extent of the residual disease after the initial surgery (i.e. 1 cm or more at the widest

TABLE 2. *The reproducibility of the subgrouping methods for ovarian clear cell adenocarcinoma as assigned by 2 observers*

	No. tumors grouped			
Subgroup	Observer 1 (H.S.)	Observer 2 (S.Y.)	% agreement (κ value)	No. tumors grouped after consensus (%)
Group A	41	50		46 (29)
Group B	84	77	88.7 (0.82)	79 (50)
Group C	34	32		34 (21)

TABLE 3. *Correlation of the postconsensus histological grade with clinical stages of the disease, residual tumor, and response to chemotherapy*

	No. tumors grouped (%)			
Parameters	Group A	Group B	Group C	*P*
(A) Clinical stage*				
I (n = 85)	24 (28)	48 (56)	13 (15)	0.159
II (n = 22)	4 (18)	10 (45)	8 (36)	
III (n = 46)	17 (37)	17 (37)	12 (26)	
IV (n = 6)	1 (17)	4 (67)	1 (17)	
(B) Residual tumor after initial surgery				
Absent (n = 117)	34 (29)	62 (53)	21 (18)	**0.017**
<1 cm (n = 19)	7 (37)	10 (53)	2 (11)	
≥1 cm (n = 23)	5 (22)	7 (30)	11 (48)	
(C) Response to chemotherapy				
CR/PR (n = 12)	4 (33)	6 (50)	2 (17)	0.112
SD/PD (n = 23)	5 (22)	8 (35)	10 (43)	

Bold numbers indicate a statistically significant difference.
*Stages of disease defined by the International Federation of Gynecology and Obstetrics.

diameter) was documented more frequently in Group C tumors (32%, 11 of 34) than in Group A tumors (11%, 5 of 46) or Group B tumors (9%, 7 of 79) ($P = 0.017$), as shown in Table 3.

Of the 12 tumors that were defined as having responded effectively (CR or PR) to postoperative chemotherapy, only 2 (17%) were grouped in Group C, whereas 10 of the 23 tumors that were defined as SD or PD (43%) were grouped in Group C. Group C tumors tended to be more frequent in the SD or PD groups than in the effective response groups, but the difference was not statistically significant ($P = 0.112$), as shown in Table 3.

Survival Analysis

For the cases including all clinical stages, patients with Group C tumors had a significantly worse outcome (42.5%, 5-yr survival rate) than those with Group A tumors (5-yr survival rate, 81.9%; $P = 0.00069$ by log-rank test) or Group B tumors (5-yr survival rate, 73.2%; $P = 0.0044$ by log-rank test; Fig. 4A). Although patients with Group A tumors tended to have better outcomes than those with Group B tumors, but the difference was not statistically significant ($P = 0.247$).

Patients with Group A tumors had excellent prognoses (5-yr survival rate, 100%), and they showed statistically significant differences in overall survival when compared with patients with Group B tumors (5-yr survival rate, 82.1%; $P = 0.024$ by log-rank test) and those with Group C tumors (5-yr

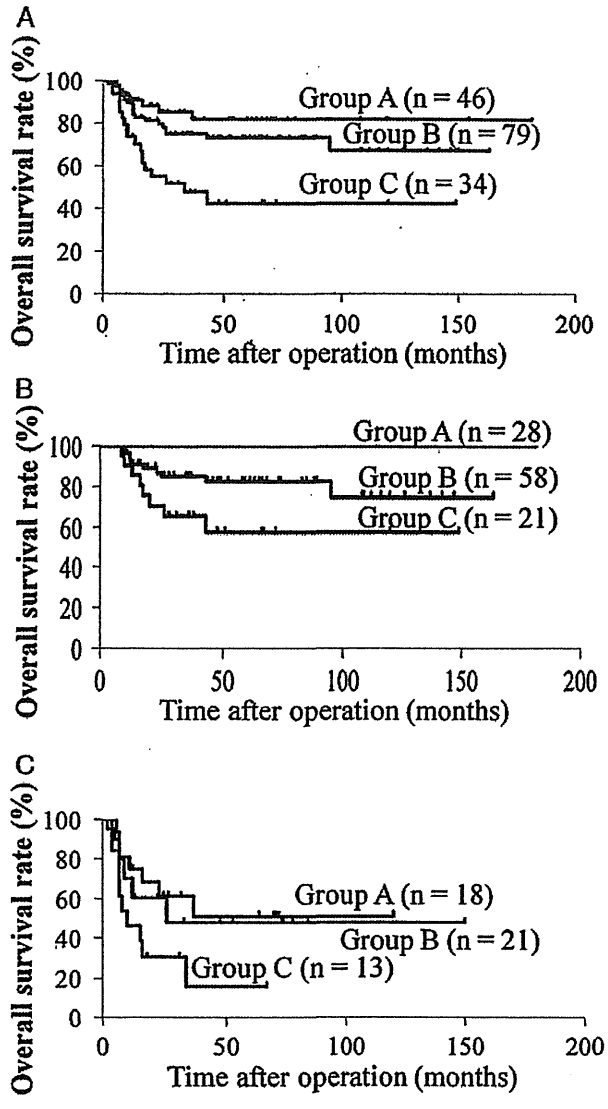

FIG. 4. Overall survival curves for (A) 159 patients with ovarian clear cell adenocarcinoma (CCA) of various stages, (B) 107 patients with early-stage CCA (stage I and II), and (C) 52 patients with advanced CCA (stage III and IV). Curves are stratified into Group A (black lines), Group B (blue lines), and Group C (red lines) by the proposed 3-tier grading system.

survival rate, 57.2%; $P = 0.00054$ by log-rank test) for the early-stage diseases (FIGO stage I or II), as shown in Figure 4B. Moreover, patients with Group B tumors had better prognoses that were near significant than those with Group C tumors ($P = 0.056$ by log-rank test; $P < 0.001$ by generalized Wilcoxon test).

For the advanced-stage diseases (FIGO stage III or IV), patients with Group A tumors had similar prognoses to those with Group B tumors (51.1% vs. 48.1% 5-yr survival rate respectively, $P = 0.671$), as shown in Figure 4C. In contrast, patients with Group C tumors had a significantly worse outcomes (15.4% 5-yr survival rate) than those with Group A or B tumors, and there were statistically significant differences between Group A and Group C tumor outcomes ($P = 0.043$ by log-rank test), as shown in Figure 4C.

TABLE 4. *Cox multivariate model estimates of prognostic factors*

Variables	*P*	RR (95% CI)
(A) Combination 1		
FIGO stage (III-IV vs. I-II)	0.050	2.38 (0.99-5.66)
Residual tumor (present vs. absent)	**0.011**	3.04 (1.30-7.13)
Group A (vs. Group B or C)	**0.018**	0.38 (0.17-0.85)
(B) Combination 2		
FIGO stage (III-IV vs. I-II)	0.051	2.33 (0.99-5.48)
Residual tumor (present vs. absent)	**0.016**	2.82 (1.21-6.55)
Group C (vs. Group A or B)	**0.0014**	2.69 (1.47-4.92)

Bold numbers indicate a statistically significant difference.

A multivariate analysis that included clinical stages as defined by FIGO (stages III to IV vs. I to II), presence of residual tumors after the initial surgery (presence regardless their size vs. absence), and histological grouping defined in this study (Group A vs. others; Group C vs. others) was performed using the Cox proportional hazard model. Consequently, Group A and Group C tumors were identified as favorable [relative risk (RR) = 0.376] and unfavorable (RR = 2.688) significant prognostic factors for overall survival ($P = 0.018$ and 0.0014, respectively), independent of the clinical stage of disease and the presence of residual tumors (Table 4).

DISCUSSION

The importance of the clinical stages of disease and presence (or extent) of residual tumors after initial surgery as prognostic factors in ovarian CCA is universally accepted (8,10,11,13,17,18). However, the significance of histological grading for CCA has been questioned. Although several studies have shown that a histological parameter, that is, prominent specific growth architecture of a tumor or mitotic index of tumor cells, could be an important prognostic factor (12,17) for CCA, others have failed to demonstrate this importance (8,17,18).

A number of studies have found that the degree of differentiation in ovarian carcinomas is important in prognosis, but there seems to be less agreement on how to assess the extent of tumor differentiation. As mentioned earlier, the usual architectural grading

systems are based on the fractions of solid and papillo-glandular structures or on the fractions of tubulo-cystic (low-grade), papillary (medium-grade), and solid (high-grade) structures (14,15). However, there is certainly some overlap of glandular, cystic, and papillary growth patterns and of glandular or papillary growth and solid growth patterns in ovarian CCA. Therefore, determining the fraction of growth architectural patterns is usually problematic, resulting in difficulties in determining tumor differentiation for CCA.

In 1998, Shimizu et al. from the Silverberg group (15) proposed a grading system as an analogy to the one used for breast carcinomas and found that their system provided valuable prognostic information on ovarian carcinomas. Furthermore, they claimed that it could be used irrespective of the histological subtypes (15). However, the results from Silverberg's group (15) and our earlier studies (16,19) indicated that the Shimizu-Silverberg grading system was not particularly useful in predicting the prognosis of patients with CCA. Therefore, CCA would require a specific grading method separate from other histological subtypes, and we have demonstrated such a system here.

This study shows that the newly proposed grouping system can be easily applied to the histological evaluation of ovarian CCAs and that it has a strong correlation with prognosis of patients with CCA even when the clinical stages are matched. Tumor cell types, that is, clear cell, hobnail, flattened or oxyphilic, cytological atypia, and mitotic activity were not considered in this study. This is because, with the exception of a few cases, a mix of various cell types exist within a tumor and it is often difficult to draw a line between these cell types. Moreover, our earlier study showed a tendency for CCA cells to possess relatively uniform nuclear morphology (usually high-grade nuclear features) and mitotic activity, usually with a low mitotic index (16,19). Our experience with the earlier series revealed that the reproducibility of both nuclear grade and mitotic index is very poor (16,19). Therefore, it is questionable whether scores of nuclear atypia or mitotic activity should be included in the grading methods for CCA in a clinical setting.

Characteristic points on the newly proposed system for ovarian CCA are as follows. First, we created a unique subgrouping system based primarily on the assessment of tumor growth architectures, and we found that this method could be performed at low magnification using 4× or 10× lenses. The subgroup was identified from the least differentiated area within a tumor and CCAs were classified into 3 subgroups (Group A, B, and C). These results may support the idea that the least differentiated tumor components in a tumor, even if these components are not prominent, determine the clinical behavior of ovarian CCA; the tumors consisting mostly of well-differentiated histology constitute a relatively favorable prognostic subgroup of ovarian CCA. Second, the new subgrouping system was simple and highly reproducible. In this series, a reproducibility rate of approximately 90% (0.82 κ value) was obtained from the observers. The success in achieving these results may be based on the existence of an easily recognizable parameter for assigning these tumors. Although histological grading results are often difficult to reproduce, Collan et al. (20) pointed out that variation in grading between observers becomes minimal when the number of criteria in the system is reduced. Further studies on reproducibility using this method among other investigators have been planned. Finally, this method could divide the patients with CCA into 3 distinct clinical behaviors of tumors, namely, patients in low-risk, intermediate-risk, and high-risk groups that have not been recognized previously, especially for the patients with early-stage disease.

The fact that the proposed histological grouping system worked well in Stage I to II diseases, the outcome of which was mainly affected by surgery, indicates that this grade might correctly reflect the biological behavior of the tumor cells. Approximately half the patients with CCA have the disease confined to the ovaries (FIGO stage I) or the pelvis (FIGO stage II) and are theoretically curable by surgery alone; however, 12% to 45% of these patients die within 5 years of initial diagnosis (2,13,17). The identification of subgroups with adverse prognoses from the outset (i.e. low-risk, intermediate-risk, and high-risk groups) would be of paramount clinical significance. Stages I to II, low-grade (Group A) tumors are accompanied by a 5-year survival rate of 100%, whereas the rate for stage I to II, high-grade (Group C) tumors is 57.2%. This suggests that CCAs entirely composed of well-differentiated histology, namely, low-grade CCAs (CCAs of Group A), would not require intensive postoperative chemotherapies, whereas tumors with less-differentiated histology, namely, intermediate to high-grade CCAs (CCAs of Group B or C), require more intensive and, probably, systemic chemotherapy, despite the detection at an early clinical stage.

In summary, we have developed a novel 3-tier grading system for ovarian CCAs, and this grading method permitted great prognostic impact and interobserver reproducibility. This system should be tested in other studies to validate its reproducibility and use for segregating patients into different prognosis groups, similar to those identified in this study. Although the treatment recommendations that we have described are reasonable based on the findings in this study, this study was not designed to address treatment issues. Specifically, whether this grading system can provide similar prognostic information for patients receiving the same treatment modalities remains to be answered in further studies.

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ORIGINAL ARTICLE

Neoadjuvant chemotherapy using platinum- and taxane-based regimens for bulky stage Ib2 to IIb non-squamous cell carcinoma of the uterine cervix

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Abstract
Purpose There are no reports on the use of neoadjuvant chemotherapy (NAC) in non-squamous cell cervical carcinoma. We examined the effectiveness and safety of paclitaxel/carboplatin (TC) and docetaxel/carboplatin (DC).
Methods Stage Ib2 to IIb disease was present in 23 patients scheduled for radical hysterectomy. We administered 1–3 courses of either the TC or the DC regimen. Antitumor effects were found superior by Response Evaluation Criteria in Solid Tumors. Safety was assessed with National Cancer Institute Common Terminology Criteria for Adverse Events.
Results Median age was 50 years (range 32–63 years), with stage Ib2 in 6 cases (26.1 %) and IIb in 17 cases (73.9 %). Complete response was achieved in 5 cases (21.7 %), partial response in 13 (56.5 %), stable disease in 5 (21.7 %); the response rate was 78.3 %, and surgery completion rate was 78.3 %. Leukopenia or neutropenia ≥grade 3 was seen in 12 (52.2 %) and 21 (91.3 %) cases, respectively, with grade 3 febrile neutropenia in 2 cases (8.7 %) and no anemia or thrombocytopenia ≥grade 3. Median progression-free survival was 26 months (95 % CI, 13.5–38.5 months); median overall survival was 35 months (95 % CI, 20.9–49.1 months).
Conclusion NAC for non-squamous cell cervical carcinoma showed potent anti-tumor effects and manageable adverse events.

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Introduction

The methods used to treat bulky stage Ib2 to IIb cervical cancers differ between Japan and Western countries. In Western countries, concurrent chemoradiation therapy (CCRT) has been recommended as a standard treatment for such tumors, based on the results of multiple large-scale randomized trials and meta-analyses [1–7]. In Japan, Korea, and Italy, among other countries, the neoadjuvant chemotherapy (NAC) approach has been introduced to clinical practice and is extensively utilized [8, 9]. An Italian phase III, controlled study involving patients with locally advanced stage Ib2 to IIb squamous cell carcinoma of the cervix showed that NAC prior to radical hysterectomy improves patient outcomes compared with conventional radiation therapy alone [10].

There are no previous reports on the use of NAC for bulky non-squamous cell carcinoma of the cervix. We present the results of an ongoing pilot study on its efficacy and safety.

Subjects and methods

Subjects

We studied 23 patients with locally advanced non-squamous cell carcinoma of the uterine cervix (clinical stage Ib2 to IIb) between January 2002 and September 2011. All patients were scheduled to undergo radical hysterectomy and gave informed consent for this study.

Inclusion criteria

The following inclusion criteria were employed: (1) histologically verified non-squamous cell carcinoma of the uterine cervix; (2) locally advanced disease, stage Ib2–IIb; (3) between 20 and 74 years of age; (4) Eastern Cooperative Oncology Group performance status 0–2; (5) no prior treatment; (6) presence of a measurable bulky mass in the uterine cervix on magnetic resonance imaging (MRI); (7) hematologic and biochemical findings within the following parameters, WBC count $\geq$4,000/mm^3, neutrophil count $\geq$2,000/mm^3, platelet count $\geq$100,000/mm^3, hemoglobin $\geq$10.0 g/dL, AST and ALT levels $\leq$2 times the upper limit of normal reference range, serum total bilirubin level $\leq$1.5 mg/dL, serum creatinine $\leq$1.5 mg/dL, and creatinine clearance $\geq$60 mL/min; (8) life expectancy $\geq$6 months; and (9) written informed consent personally given by the subject.

Exclusion criteria

Exclusion criteria were as follows: (1) overt infection; (2) serious complication(s), for example, cardiac disease, poorly controlled diabetes mellitus, malignant hypertension, bleeding tendency; (3) multiple active cancers; (4) interstitial pneumonia or pulmonary fibrosis; (5) pulmonary effusions; (6) history of unstable angina or myocardial infarction within 6 months after registration, or a concurrent serious cardiac arrhythmia requiring treatment; (7) contraindications to treatment with paclitaxel, docetaxel, or carboplatin; (8) intestinal paralysis or ileus; (9) pregnancy, breast-feeding, or desire for future pregnancy; (10) history of serious drug hypersensitivity or drug allergy; and (11) judged unsafe for participation by the attending physician.

Medication administration and criteria for modification

Regimen

The choice of regimen was left to the attending physician. Paclitaxel/carboplatin (TC) therapy was administered to 4 patients and DC therapy to 19 patients. Courses of treatment were administered 21 days apart, with a intravenous paclitaxel dose of 175 mg/m^2 or a docetaxel dose of 70 mg/m^2 administered on Day 1, and intravenous carboplatin with area under the curve (AUC) 6 mg/mL per min also administered on Day 1. As a rule, maximum 3 courses of treatment were administered to each patient.

Criteria for initiating the second course of treatment

The second course was postponed by a maximum of 2 weeks when blood analysis performed within 2 days prior to the planned start did not satisfy the following criteria: (1) neutrophil count $\geq$1,000/mm^3; (2) platelet count $\geq$75,000/mm^3.

Carboplatin dose-reduction criteria

The carboplatin dose for the second course was reduced from AUC 6 mg/mL per min to AUC 5 mg/mL per min if the patient experienced grade 4 thrombocytopenia or grade 3 thrombocytopenia accompanied by bleeding. If signs of toxicity remained after this dose reduction, the third course of treatment was reduced to AUC 4.

Paclitaxel dose-reduction criteria

The paclitaxel dose for the second course was reduced from 175 to 135 mg/m^2 in patients exhibiting grade 2 or higher severe peripheral nerve toxicity during the first course. If this grade of nerve toxicity persisted after the dose reduction, the paclitaxel dose for the third course was reduced to 110 mg/m^2.

Docetaxel dose-reduction criteria

The docetaxel dose for the second course was reduced from 70 to 60 mg/m^2 if the patient experienced grade 4 neutropenia lasting 7 days or longer or febrile neutropenia lasting 4 days or longer. If signs of toxicity remained after this dose reduction, the docetaxel dose for the third course was reduced to 50 mg/m^2.

Supportive therapy

A granulocyte colony-stimulating factor (G-CSF) preparation was administered to patients who developed grade 4 neutropenia during the first course of NAC. These patients were permitted prophylactic G-CSF during the second and subsequent courses of NAC. Anti-emetics were used for the preventive purpose.

Primary treatment

Patients with stage Ib2–IIb cervical carcinoma underwent radical hysterectomy unless the tumor responded to preoperative treatment with progressive disease (PD), at which time the tumor was up-staged. In cases in which surgery was not possible, CCRT was adopted.

Postoperative therapy

Postoperative radiotherapy, postoperative chemotherapy, or CCRT was additionally administered in patients with a positive surgical margin at the vaginal stump,

lymphadenopathy, invasion of the cardinal ligament, or evident invasion of the vasculature.

Outcome evaluation

The primary endpoint was anti-tumor response. Secondary endpoints comprised adverse events, the surgery completion rate, the progression-free survival (PFS) period, and the overall survival (OS) period. Hematologic tests and urinalysis were performed before the start of treatment and, as a rule, once weekly after starting treatment. Electrocardiograms and chest radiographs were obtained before the start and at the end of treatment.

Evaluation of anti-tumor response

Anti-tumor response was evaluated using Response Evaluation Criteria in Solid Tumors guidelines. The baseline MRI findings were compared with the findings at the conclusion of treatment. For our efficacy evaluation, we adopted the best rating, without incorporating the response period.

Evaluation of adverse events

Adverse events were evaluated employing the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analysis

Progression-free survival (PFS), defined as the time from the start of the study treatment to documented tumor progression or death, and overall survival (OS), defined as the time from the start of treatment to the date of death, were calculated by the Kaplan–Meier method. The statistical data were obtained using StatMate III.

Results

Background variables

The median age of the 23 patients was 50 years (range 32–63 years). The performance status was 0 in 18 patients (78.3 %), and in 5 patients, the performance status was 1 (21.7 %). The clinical stage was Ib2 in 6 cases (26.1 %) and IIb in 17 cases (73.9 %). The histological type was mucinous adenocarcinoma in 10 cases (43.5 %), endometrioid adenocarcinoma in 5 (21.7 %), clear cell adenocarcinoma in 1 (4.3 %), and adenosquamous carcinoma in 7 (30.4 %). One course of NAC was administered in 1 patient (4.3 %), 2 courses in 17 patients (73.9 %), and 3 courses in 5 patients (21.7 %). The regimens comprised TC therapy in 4 cases (17.4 %) and DC therapy in 19 cases (82.6 %) (Table 1).

Anti-tumor response

A complete response was noted in 5 cases (21.7 %), partial response in 13 (56.5 %), and stable disease in 5 (21.7 %), with a overall response rate of 78.3 %. In subgroup analysis, the overall response rate of TC therapy and DC therapy was 100 and 73.7 %, respectively (Table 2).

Adverse events

Grade 3 or higher severe leukopenia or neutropenia was seen in 12 (52.2 %) and 21 (91.3 %) cases, respectively. Grade 3 febrile neutropenia was noted in 2 cases (8.7 %). The G-CSF preparation was used in 13 (56.5 %) of the 23 patients; it was administered during 19 (38.8 %) of the 49 total cycles. The mean duration of G-CSF treatment during each course was 2.6 days. No patients experienced grade 3 or higher severe anemia or thrombocytopenia. The only sign of grade 3 or higher severe non-hematologic toxicity was nausea, seen in 1 case (4.3 %). No patients had signs of grade 2 or higher severe neurotoxicity (Table 3).

In 3 cases (13.0 %), the second course of treatment was postponed due to a low neutrophil count; in all 3 patients, the second course was initiated within 7 days of its scheduled time. Both patients (10.0 %) with grade 3 febrile neutropenia for 4 days or longer had received DC therapy prior to the development of this complication. In these 2 cases, doses were reduced for the second course of treatment: docetaxel from 70 to 60 mg/m^2 and carboplatin from AUC 6 to AUC 5.

Table 1 Patient characteristics ($n = 23$)

Median age years [range]		Cell type	
50 [32–63]		Mucinous	10 (43.5 %)
Performance status at entry		Endometrioid	5 (21.7 %)
0	18 (78.3 %)	Clear cell	1 (4.3 %)
1	5 (21.7 %)	Adenosquamous	7 (30.4 %)
2	0 (0 %)	Regimen	
FIGO stage at initial diagnosis		DC	19 (82.6 %)
Ib2	6 (26.1 %)	TC	4 (17.4 %)
IIa	0 (0 %)	Number of cycles	
IIb	17 (73.9 %)	1	1 (4.3 %)
		2	17 (73.9 %)
		3	5 (21.7 %)

DC docetaxel + carboplatin, *TC* paclitaxel + carboplatin

Table 2 Response

	CR	PR	SD	PD	Overall response
Total	5	13	5	0	18 (78.3 %)
TC	1	3	0	0	4 (100 %)
DC	4	10	5	0	14 (73.7 %)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *TC* paclitaxel + carboplatin, *DC* docetaxel + carboplatin

Table 3 Adverse events of TC/DC therapy

$n = 23$	Grade				
	1	2	3	4	≧3 (%)
Leukopenia	2	9	11	1	12 (52.2)
Neutropenia	1	1	7	14	21 (91.3)
Thrombocytopenia	11	0	0	0	0
Anemia	11	12	0	0	0
Nausea	11	3	1	0	1 (4.3)
Vomiting	5	3	0	0	0
Diarrhea	2	0	0	0	0
Neurotoxicity	18	0	0	0	0
Dyspnea	3	0	0	0	0
Fibrile neutropenia	0	0	2	0	2 (8.7)

TC paclitaxel + carboplatin, *DC* docetaxel + carboplatin

Surgery completion and adjuvant therapy

Radical hysterectomy after NAC was completed in 18 of the 23 patients, giving a surgery completion rate of 78.3 %. Adjuvant therapy after radical hysterectomy consisted of no treatment in 3 cases (13.0 %), radiotherapy in 2 cases (8.7 %), chemotherapy in 15 cases (65.2 %), and CCRT in 3 cases (13.0 %).

Survival

The median follow-up period was 31 months (range 9–90 months). The median progression-free survival period was 26 months (95 % CI, 13.5–38.5 months), and the median overall survival period was 35 months (95 % CI, 20.9–49.1 months) (Fig. 1). The 5 patients in whom surgery was not complete died of their primary disease within 35 months. Their median PFS and OS were 8 months (3–12 months) and 21 months (10–35 months), respectively.

Discussion

The incidence of non-squamous cell carcinoma of the uterine cervix has been steadily rising in Japan, currently accounting for approximately 10–15 % of all cervical cancer cases. Lymph node metastasis is more frequent with this disease, compared with invasive squamous cell carcinoma [11], and its sensitivity to radiotherapy and chemotherapy is considered to be lower [12]. Thus, squamous and non-squamous cell carcinomas must be analyzed separately. It is advisable and desirable to try new therapeutic strategies in non-squamous cell carcinoma, but the number of published studies involving this type of cervical cancer is small, with the number of cases analyzed in these reports also small. Thus, no high-level evidence regarding treatment has been obtained for this type of cervical carcinoma.

The response rates of adenocarcinoma are reportedly 20 % to cisplatin [13], 15 % to ifosfamide [14], 14 % to 5-fluorouracil [15], and 12 % to oral etoposide [16]; these response rates are lower than those of squamous cell carcinoma. According to Curtin et al. [17], however, the response rate of adenocarcinoma to paclitaxel is as high as 31 %, even when the agent is used independently. Docetaxel has also been attracting interest as an agent of NAC. Nagao et al. evaluated the efficacy of combined chemotherapy using a DC regimen (docetaxel 60 mg/m^2 and carboplatin at AUC 6 on day 1, repeating the combination every 21 days) in 17 patients with advanced or recurrent cervical cancer, including 6 with adenocarcinoma and 1 with adenosquamous carcinoma. A partial response was obtained in 6 of the 7 cases with adenocarcinoma (including the case of adenosquamous carcinoma); the response rate was 86 % [18]. Considering these findings, we conducted a pilot study involving standard regimens of TC and DC, conventionally used for the treatment of ovarian cancer.

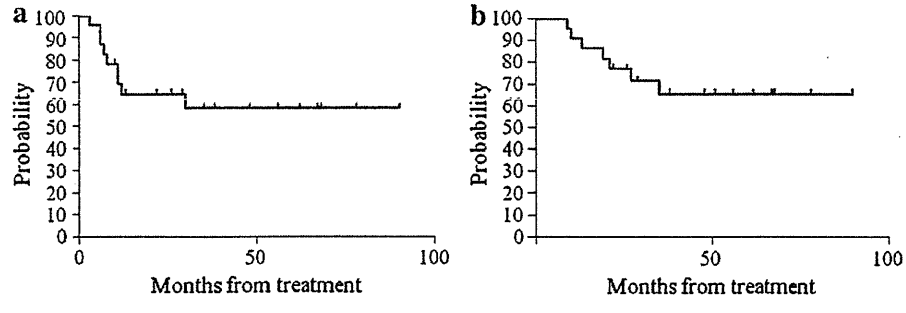

Fig. 1 Kaplan–Meier curves for progression-free survival (**a**) and overall survival (**b**). The median PFS for all patients was 26 months (95 % CI, 13.5–38.5 months), and the median OS was 35 months (95 % CI, 20.9–49.1 months)