similar. An international phase III study to compare CPT-P and TC as adjuvant chemotherapy for stage I-to-IV CCC has completed enrollment (GCIG/JGOG3017). The results will be reported in 2014.

Adjuvant radiotherapy may have a role in the adjuvant treatment of early stage CCC. A retrospective series, which included 375 women with CCC, endometrioid and mucinous, found a benefit in survival for women treated with adjuvant chemotherapy plus whole abdominopelvic radiotherapy compared with chemotherapy alone.[27] The benefit seems to be mainly in high-risk stage 1C (positive peritoneal cytology and ovarian surface disease) and stage II disease.[28] These findings require confirmation in a prospective randomized trial.

METASTATIC DISEASE AND RELAPSE

Pattern of Relapse

The prognosis of recurrent CCC is very poor, even compared with that of recurrent serous adenocarcinoma with 5-year OS rates of 22.5% and 32.4%, respectively (P = 0.0007) and median OS of 25.3 versus 42.0 months. The 5-year postrecurrence survival rate is only 13.2% for CCC compared with 18.2% for HGS ($P < 0.0001$), with a median postrecurrent survival of 10.0 versus 18.9 months.[29] Recurrence rates of CCC were 29%, 30%, 62%, and 73% for stages I, II, III, and IV, respectively, with a median time to recurrence for the stages I and II of 12.2 months.[1] The prognosis is particularly poor relative to HGS tumors, where there is residual tumor after initial surgery.[1,29]

The pattern of recurrence also differs from HGS with higher rates of relapse in the lymph nodes (pelvic, para-aortic, and other lymph nodes) (40% vs 7%, $P < 0.001$) and parenchymal organs (liver, lung, bone, spleen, brain and others) (40% vs 13%, $P < 0.01$).[30]

Treatment

Treatment of recurrent CCC has, to date, followed the same protocols as are used for other recurrent ovarian epithelial carcinomas.[31] However, recurrent CCC is very resistant to chemotherapy with response rates of less than 10%.[32] Unlike in ovarian cancer in general, platinum-free interval does not seem to predict for further chemotherapy sensitivity. Despite evidence that recurrent CCC is resistant to subsequent chemotherapies,[32] no correlation between an efficacy of the second-line chemotherapy and histopathological types has been yet revealed.[33] However, this may be due to the small numbers of clear cell cancers included in trials of recurrent disease. For example, in a phase III study of paclitaxel plus carboplatin versus liposomal doxorubicin plus carboplatin in platinum-sensitive recurrence, the proportion of serous adenocarcinoma was 72%, whereas that of clear cell adenocarcinoma was only 2.8%.[34] In a phase III trial, liposomal doxorubicin was compared with gemcitabine in platinum-resistant recurrent cases; the proportion of serous adenocarcinoma was 80%, whereas that of clear cell adenocarcinoma was only 6.5%.[35]

Given the limited benefit from cytotoxic drugs, there is now great interest in the development of molecular targeted therapy for the treatment of CCC.

FUTURE DIRECTIONS

Table 1 lists the potential therapeutic targets in CCC. The continued development of targeted agents in the treatment of CCC requires investigation of a number of areas in the laboratory. The mechanisms of resistance to targeted agents are largely unknown, but an understanding of these will be essential for clinical development and application.

The lack of a mouse model of CCC is another important issue. For the deeper understanding of the pathogenesis of CCC as well as the more accurate evaluation of the antitumor activity of particular agents against CCC, a mouse model of CCC needs to be developed in the future.

Intelligently designed clinical trials are essential for the clinical development of novel therapies. There are a number of promising agents, but the optimal way to sequence and/or combine them needs to be established. Tumors require a vascular blood supply to grow beyond 2 to 3 mm; thus, subclinical ovarian tumors that develop after complete clinical response to

TABLE 1. Potential therapeutic targets in CCC

Targets	Roles in Tumor Development	Comments
Phospho-AKT	Proliferation/survival	Frequently in CCC and SAC
Phospho-mTOR	Proliferation/angiogenesis/metabolism	Frequently expressed in CCC
HIF-1α	Angiogenesis, adaptive response to hypoxia	Frequently expressed in CCC and SAC
VEGF	Angiogenesis	Frequently expressed in CCC and SAC
HNF-1β	Detoxification, chemoresistance, and survival	Frequently expressed in CCC
Annexin A4	Detoxification, chemoresistance	Frequently expressed in CCC
Osteopontin	Survival/migration/invasion	Frequently expressed in CCC and SAC
UGT1A1	Detoxification, irrinotecan resistance	Frequently expressed in CCC
IGFBP-1	Proliferation/survival	Frequently expressed in CCC
IGF2BP3	Translation, migration	Frequently expressed in CCC and SAC
IL-6/STAT-3	Proliferation/antiapoptosis/angiogenesis	Frequently expressed in CCC

SAC, serous adenocarcinoma.

first-line chemotherapy require angiogenesis for continued proliferation. Considering the significant antiproliferative and antiangiogenic activities of targeted agents, the activity of these agents as a maintenance therapy for preventing or delaying the development of recurrent disease needs to be investigated.

As the PI3K/AKT/mTOR signaling pathway is hyperactivated in CCC, strategies aimed to inhibit this pathway may have therapeutic activity for CCC.[36] Not only using them as a monotherapy, combination treatments may also be an attractive strategy to investigate in trials. For example, patients might start on mTOR-targeting therapy and then switch to VEGF-targeting therapy on progression. Other avenues of research include sequencing mTORC1 inhibitor initially and then switching to an mTORC1/2 inhibitor. Considering the frequent *PIK3CA* mutation in CCC,[12] dual inhibitors targeting PI3K, AKT in the mTOR pathway, are also promising. The efficacy and toxicities of simultaneous inhibition of different signaling pathways should be investigated. Another potential avenue is the combination of targeted agents with effective cytotoxic agents, as targeting agents are generally cytostatic. Intriguing preclinical results suggest that trabectedin is the most effective of the existing cytotoxic agents against CCC,[37] and this may be enhanced by the addition of an mTOR inhibitor. This combination warrants further investigation in future clinical studies.

Translating preclinical findings into successful treatment for patients is challenged by issues that are common to studying targeted agents in any tumor and studying any therapy in rare tumors. First, the method of efficacy evaluation of targeted agents needs to be reassessed. As many of the targeted agents have cytostatic rather than cytotoxic effects, the traditional criteria applied to cytotoxic agents, such as RECIST, might be less applicable when determining the clinical benefit of targeted agents. Second, identifying biomarkers that can be used to predict a patient's sensitivity to the targeted agents is a critical issue. The identification of surrogate markers to monitor the activity of targeted agents is also necessary. For this purpose, future clinical studies of targeted agents must incorporate translational research.

Finally, given the rarity of and the geographical difference in the prevalence of CCC, international collaboration, mediated by the Gynecologic Cancer InterGroup, may be essential to obtain adequate patient numbers. These efforts will allow selection of the best treatment for investigation in larger-scale clinical trials. Moreover, these challenges will aid in the development of optimal, personalized targeted therapies for CCC.

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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.

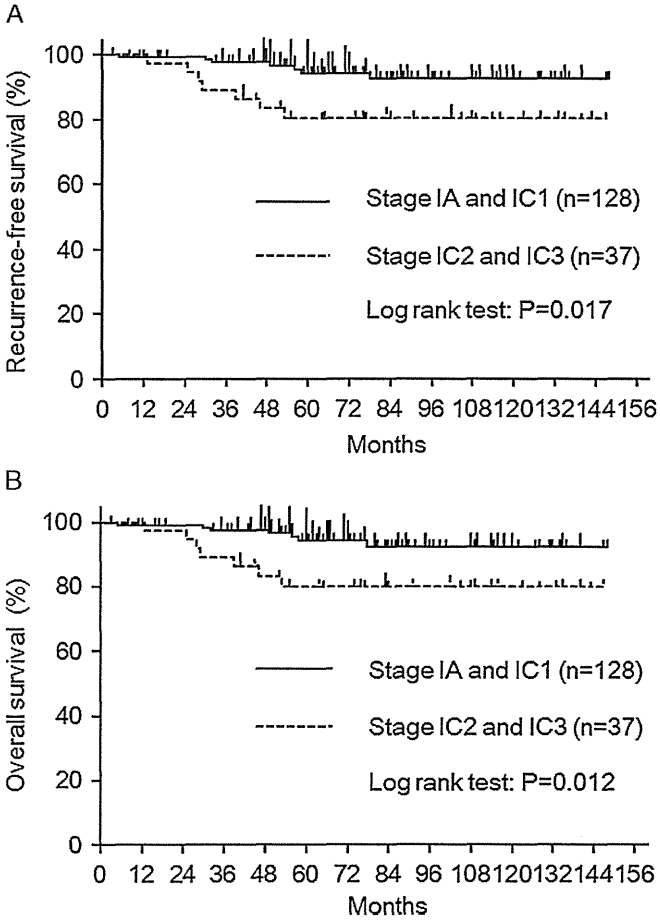

FIGURE 1. Kaplan-Meier curves for RFS (A) and OS (B) in patients with stages IA/IC1 and stages IC2/IC3. Significant differences were observed in RFS and OS between patients with stages IA/IC1 and stages IC2/IC3 (RFS: $P = 0.017$; OS: $P = 0.012$).

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

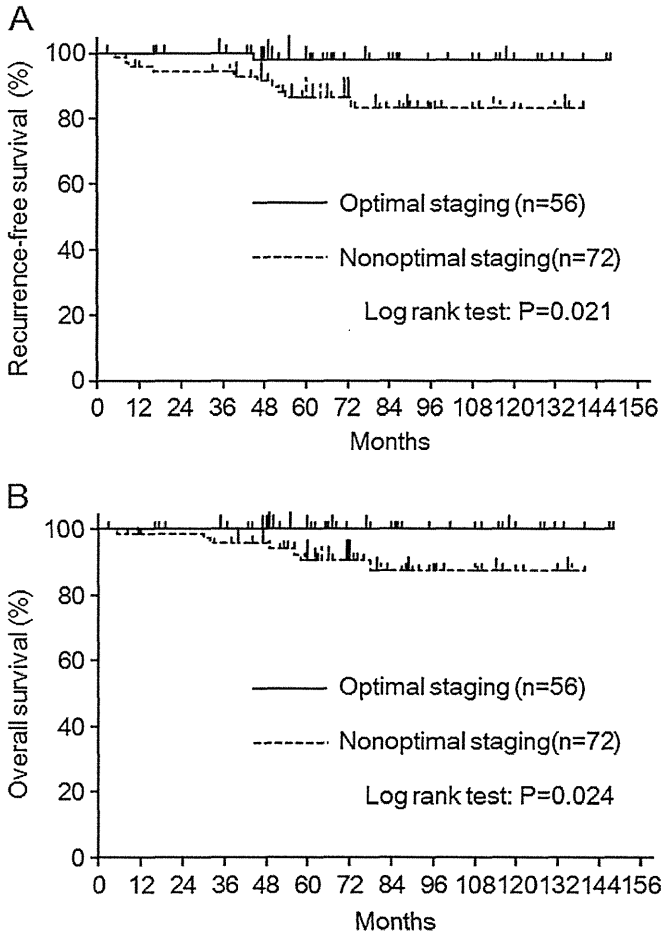

FIGURE 2. Kaplan-Meier curves for RFS (A) and OS (B) in patients with stages IA/IC1 by surgical staging category. Significant differences were observed in RFS and OS between patients optimally and nonoptimally staged (RFS: $P = 0.021$; OS: $P = 0.024$).

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

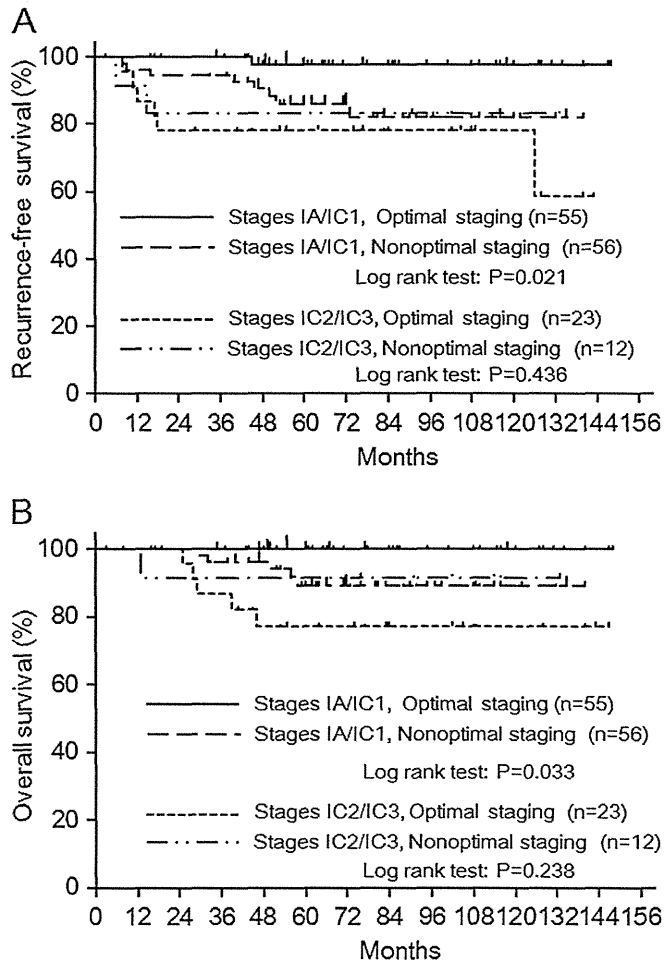

FIGURE 3. Kaplan-Meier curves for RFS and OS (B) in patients who received adjuvant chemotherapy by both stage and surgical staging category. Significant differences were observed in RFS and OS between stages IA/IC1 patients optimally and nonoptimally staged (RFS: $P = 0.021$; OS: $P = 0.033$), whereas 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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Clinical experience of J-VAC drain for skin closure in the laparotomy of obstetrics and gynecology

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Abstract

Aim: The frequency of wound dehiscence after abdominal surgery has been reported to be approximately 4–29%, and that of surgical site infections is said to be of about 20%. We examined the effectiveness of the subcutaneous J-VAC drain (JVD) in the drainage of bleeding and exudates from surgical wounds.

Material and Methods: The study was conducted on 192 patients who underwent abdominal surgery from October 2009 to February 2011, and in whom indwelling JVD were placed. During the study period, JVD (10-Fr) were placed subcutaneously on the anterior surface of the fascia in all patients. We examined the frequency of surgical wound complications.

Results: A longitudinal incision was used in 101 patients, and a transverse abdominal incision was used in 91 patients. Subjects with a subcutaneous fat thickness of 2 cm or thicker accounted for 115 patients. Subcutaneous hematoma was present in three patients, but only two patients (1%) showed dehiscence that required treatment.

Conclusions: This study revealed that subcutaneous JVD is useful for the closure of surgical incisions in gynecology and obstetrics, and that there are no limitations to their applicability.

Key word: J-VAC drain, subcutaneous drain, surgery, wound complication.

Introduction

In general abdominal surgery, there is a 4% frequency of wound dehiscence, which is increased to 29% in obese patients.[1] In addition, the frequency of surgical site infection (SSI) in patients with subcutaneous fat greater than 3 cm in thickness is 15–40%.[2] Such wound complications increase the duration of hospitalization and reduce the patient's quality of life (QOL). Furthermore, it is important to address this problem from a medical economics point of view.

Accumulation of transudate from postoperative wounds has the possibility to inhibit wound healing, resulting in SSI. In order to drain transudate from the wound, subcutaneous drains have been developed. This study retrospectively analyzed the efficacy of J-VAC drain (JVD) and its correlation with body mass index (BMI), deep subcutaneous fat thickness, skin incision method, complications, and subcutaneous suture.

The objective of the present study was to evaluate the efficacy of subcutaneous JVD for draining wound bleeding and transudate in laparotomy patients.

Methods

From October 2009 to February 2011, a JVD was inserted in 192 patients who underwent obstetrics and

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Table 1 Characteristics of the patients

Patient characteristics		
Mean age		40.9 years (19–79)
Mean body mass index		23.8 kg/m^2 (16.9–41.9)
Mean deep subcutaneous fat thickness		2.4 cm (0.5–8.0)
Operation method		Surgery for malignant tumor: 35 cases; surgery for benign tumor: 89 cases; cesarean section: 68 cases
Surgical incision	Horizontal incision	91 cases (with embedded sutures: 41 cases, without: 50 cases)
	Vertical incision	101 cases (with embedded sutures: 11 cases, without: 90 cases)

The number of vertical and horizontal incisions was similar; however, subcutaneous fat-tissue closures were carried out less often for vertical incisions.

Table 2 Cases with risk factors for wound dehiscence

Cases with risk factors for wound dehiscence	
Subcutaneous fat thickness >2 cm	115 cases
BMI > 25	61 cases (BMI > 30: 6 cases)
Malignant disease	35 cases
Previous surgical history	33 cases
Diabetes mellitus	5 cases
Cases with the above risk factors	139 cases
Cases without the above risk factors	53 cases

Subcutaneous fat of more than 2 cm in thickness was found in 115 cases. Fifty-three cases had no risk factors. BMI, body mass index.

gynecology laparotomy at Kousei General Hospital in Tokyo. During this period, all patients were treated with JVD regardless of their subcutaneous fat thickness, BMI, or surgical procedure.

Characteristics of the patients are provided in Table 1. The mean age of the 192 patients was 40 years (19–79 years); the mean BMI was 24 kg/m^2 (16.9–41.9 kg/m^2); and the mean thickness of deep subcutaneous fat was 2.5 cm (0.5–8.0 cm). The surgical procedures were 68 cases of cesarean section and 35 cases of surgery for malignant tumors. The number of vertical and horizontal incisions was similar; however, subcutaneous fat-tissue closures were carried out less often for vertical incisions.

Subcutaneous fat of more than 2 cm in thickness, which was the most common risk factor for wound dehiscence, was found in 115 cases. Fifty-three cases had no risk factors, such as malignant diseases, diabetes mellitus, or surgical history (Table 2).

All cases, except for patients with allergies, received first-generation cephem antibiotics for 2 days. Patients were shaved 1 day prior to surgery, and the operative field was disinfected using isodine liquid. During wound closure, a JVD (10-Fr) was fixated on the skin 3 cm from the incision. Subcutaneous fat-tissue closure was not standardized and left to each surgeon's discretion. Deep dermal sutures were not used in all cases, and the skin was closed using staples. As a principle, the JVD was removed 3 days after insertion; however, if the amount of transudate exceeded 10 mL on day 3, the JVD was removed on day 4. Wound dehiscence was defined as a dehiscence of more than 1 cm of subcutaneous tissue; wound infection was defined by the presence of at least two of the following criteria: redness, tenderness, induration, fever, and pyogenic substances. The retrospective analysis included a correlation of the amount of postoperative drainage and wound complications with the skin incision method, deep subcutaneous fat thickness, and the use of subcutaneous fat-tissue closure. The *t*-test was used where appropriate for univariate analysis. A *P*-value of less than 0.05 was considered statistically significant.

An illustration of drain insertion is shown in Figure 1. This demonstrates that drain insertion was possible even in cases with large wounds in surgery for malignancies.

Results

The mean exudate volume of JVD was 15.75 mL on day 1 and 12.63 mL on day 2. Horizontal skin incisions had significantly increased drainage on both day 1 and day 2 (Fig. 2). A comparison between vertical and horizontal incisions in each group revealed that the use of vertical incisions in those without subcutaneous fat-tissue closure showed significantly increased drainage on both day 1 and day 2 (Fig. 3).

BMI and deep subcutaneous fat thickness were not significantly correlated with the amount of JVD drainage (Fig. 4). Even after dividing the subjects into four groups (horizontal incision with subcutaneous fat-tissue closure, horizontal incision without subcutaneous fat-tissue closure, vertical incision with

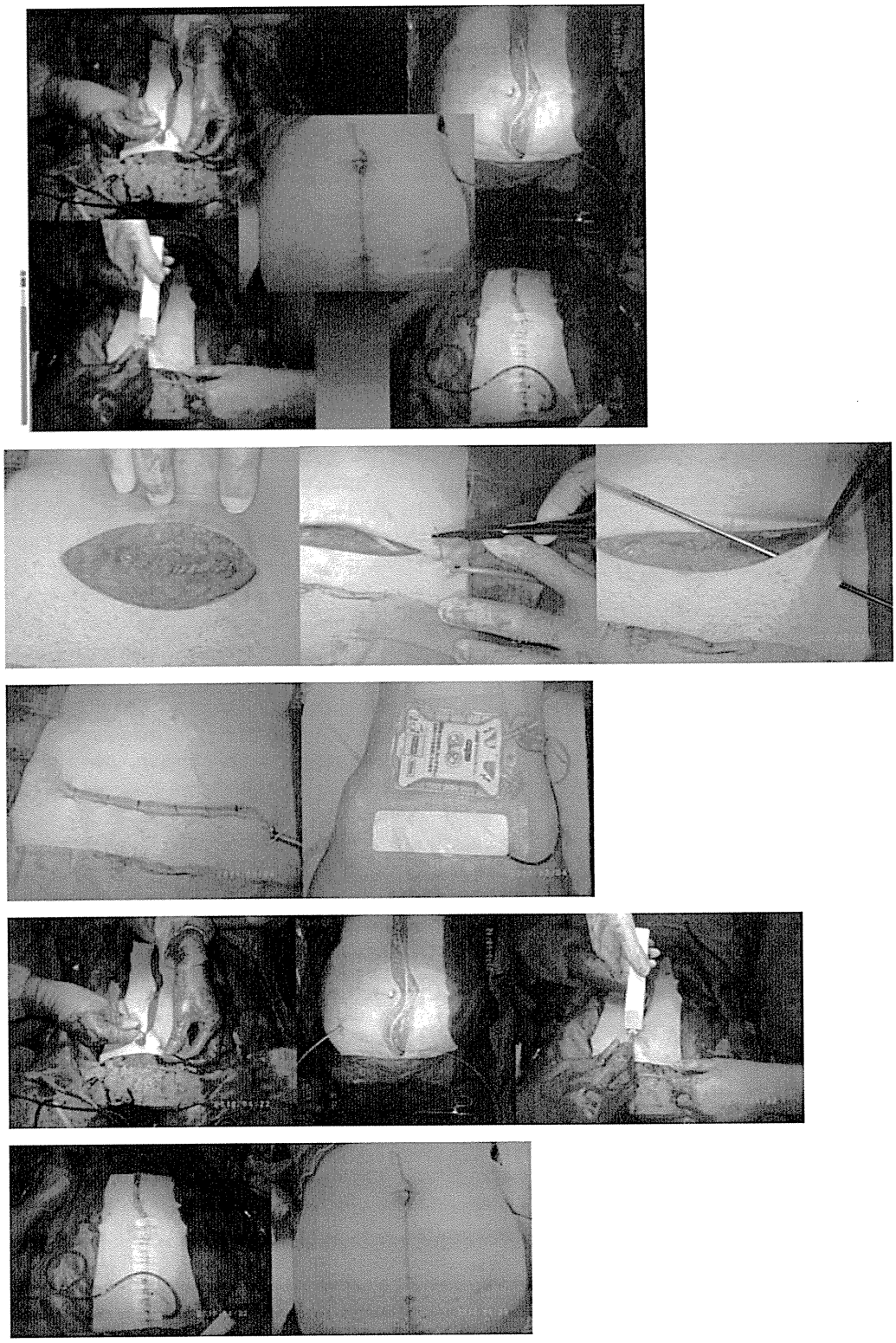

Figure 1 Actual insertion (vertical incision) method of the drain at the operation.

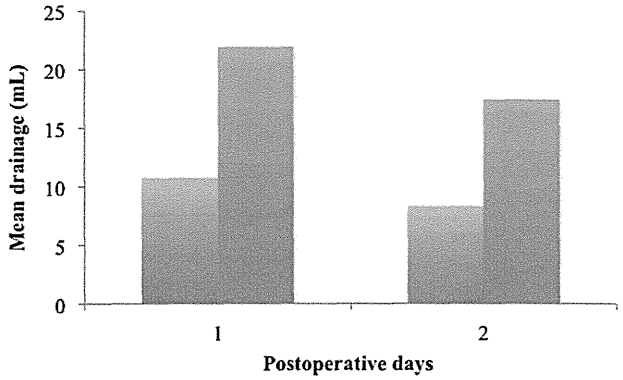

Figure 2 Amount of drainage based on skin incision method. Horizontal skin incisions had increased drainage on both day 1 and day 2. $P < 0.01$ (day 1). $P < 0.01$ (day 2). ■, vertical incision; ■, horizontal incision.

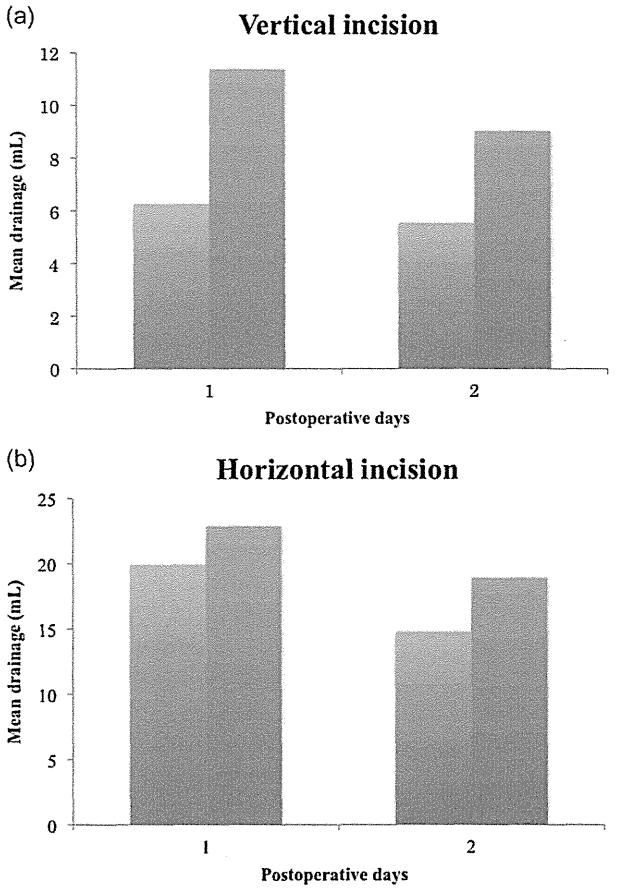

Figure 3 Amount of drainage in groups with and without subcutaneous tissue sutures using (a) vertical ($P = 0.031425$ [day 1], $P = 0.023257$ [day 2]) and (b) horizontal ($P = 0.153953$ [day 1], $P = 0.039930$ [day 2]) skin incisions. The use of vertical incisions in those without subcutaneous fat-tissue closure was correlated with increased drainage on both day 1 and day 2. ■, with suture; ■, without suture.

subcutaneous fat-tissue closure, and vertical incision without subcutaneous fat-tissue closure), there were no significant correlations between BMI or deep subcutaneous fat thickness and the amount of drainage in each group. This confirmed a lack of correlation between BMI and deep subcutaneous fat thickness with JVD drainage.

Wound dehiscence was found in two cases. In one case, 4-cm dehiscence was found with infection, and antibiotics were administered without re-suturing. A wound culture confirmed *Pseudomonas aeruginosa* infection. The other case was a 2-cm dehiscence requiring re-suturing because of thick fat layers. These were the only cases requiring further treatment. The others had only minor complications, such as subcutaneous hematoma and steatolysis, which did not require further treatment (Table 3). The mean drainage volume for all cases with complications was 27.8 mL on day 1 and 9.4 mL on day 2. Because the number of cases with complications was small, drainage volume was not analyzed as a risk factor. When complications were analyzed by the thickness of the subcutaneous fat, dehiscence occurred in those with fat thickness greater than 3 cm (Table 4).

In total, wound complications were found in five cases (2.6%), and dehiscence and infection were found in two cases (1%). All of these complications occurred in those without subcutaneous fat-tissue closure.

Discussion

JVD is a solid-core structure drain with a 3-D core, which allows the lumen to retain its round shape. Inside the lumen, there are four drainage channels (Fig. 5). Using a ditch-type structure, it allows for a wider area of contact with the surrounding tissue. The drain adjusts to collect transudate imitating the capillary vessel phenomenon. Furthermore, its flexibility allows for precise indwelling in the tissue. It is also reported to have high histocompatibility. Because there are no holes in its sides, it is easily removed with less silicon-related removal pain and drain insertion-related pain. The suction bag has an internal spring structure, which allows for constant, and sustainable negative pressure. The system not only controls clot and hematoma formation but also reduces the occurrence of delayed wound healing. Because the suction pressure is well distributed, there is a reduced risk of tissue

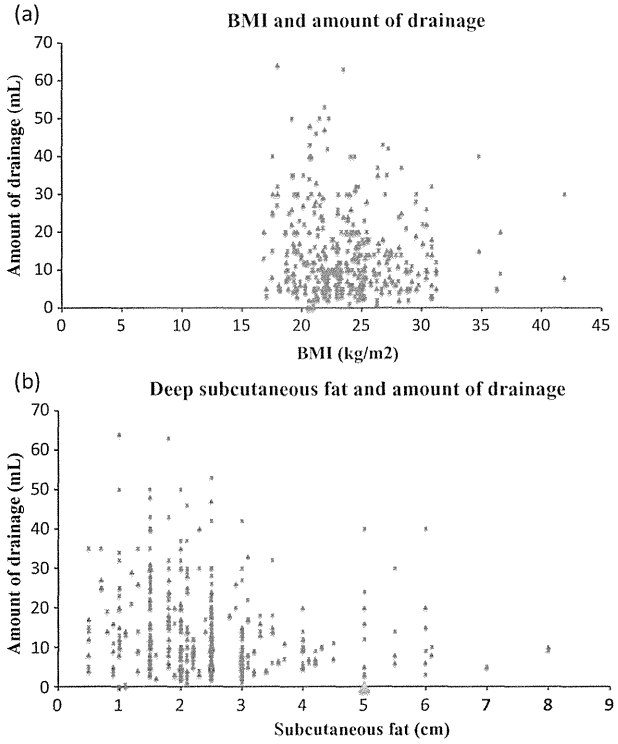

Figure 4 Amount of drainage based on (a) body mass index (BMI) (correlation coefficient –0.15681 [day 1], correlation coefficient –0.19874 [day 2]) and (b) deep subcutaneous fat thickness (correlation coefficient –0.03175 [day 1], correlation coefficient –0.14988 [day 2]). BMI and deep subcutaneous fat thickness were not significantly correlated with the amount of J-VAC drain (JVD) drainage. ✳, 24-h drainage; ▲, 48-h drainage.

damage. Also, because the retrogression prevention valve is adopted in the JVD and the diameters of the drain and needle are the same, leakage from the site of insertion is prevented and retrograde infection is reduced (Fig. 6). However, there are no reports comparing the SSI of J-VAC and SB-VAC.

Previous data showed the relation among deep subcutaneous fat thickness, wound infection rate and wound dehiscence rate.[2,3] Thicker deep subcutaneous fat was correlated with a higher frequency of wound complications. Compared to the results from other studies, our results demonstrated a lower frequency of wound complications. The reason for this discrepancy could be that subjects in previous studies were limited to those with subcutaneous fat of more than 3 cm and those who received vertical incisions.[3] In addition, a three-group comparison of the dehiscence rate between the subcutaneous drain group, the

Table 3 Surgical complications

	Age	Disease (surgical procedure)	Risk	Subcutaneous fat (cm)	BMI (kg/m^2)	Incision	Subcutaneous tissue sutures	Amount of drainage Day 1/Day 2 (mL)	Complications
1	43	Myoma uteri (TAH)	previous surgery +	1.5	19.2	Horizontal	NA	50/22	Subcutaneous hematoma (2 × 2 cm)
2	34	LPM (RSO)	NA	1	19	Vertical	NA	25/8	Subcutaneous hematoma (small)
3	64	Endometrial Cancer (RH)	NA	3	22.2	Vertical	NA	42/2	4-cm dehiscence, infection
4	35	Myoma uteri (myomectomy)	NA	5	31.3	Vertical	NA	12/5	2-cm dehiscence, re-sutured
5	63	Endometrial cancer (RH)	NA	4.3	28.8	Vertical	NA	10/10	Small steatolysis

*Wound dehiscence was found in 2 cases. In one case (case 3), 4-cm dehiscence was found with infection, and antibiotics were administered without re-suturing. A wound culture confirmed *Pseudomonas aeruginosa* infection. The other case was a 2-cm dehiscence requiring re-suturing because of thick fat layers. These were the only cases requiring further treatment. The others had only minor complications, such as subcutaneous hematoma and steatolysis, which did not require further treatment. LPM, low potential malignancy; NA, not applicable/none; RH, radical hysterectomy; RSO, right salpingo-oophorectomy; TAH, total abdominal hysterectomy.*

Table 4 Subcutaneous fat thickness and complication

Subcutaneous fat	Number	Complication
0≦ >2 cm	72	Hematoma 2 cases
2≦ >3 cm	65	
3≦ >4 cm	32	Wound dehiscence 1 case
4≦ >5 cm	11	Steatolysis 1 case
5≦ >6 cm	6	Wound dehiscence 1 case
6≦ >7 cm	4	
7≦ >8 cm	1	
8≦ >9 cm	1	
Total	192	5 cases

When complications were analyzed by the thickness of the subcutaneous fat, dehiscence occurred in those with fat thickness greater than 3 cm.

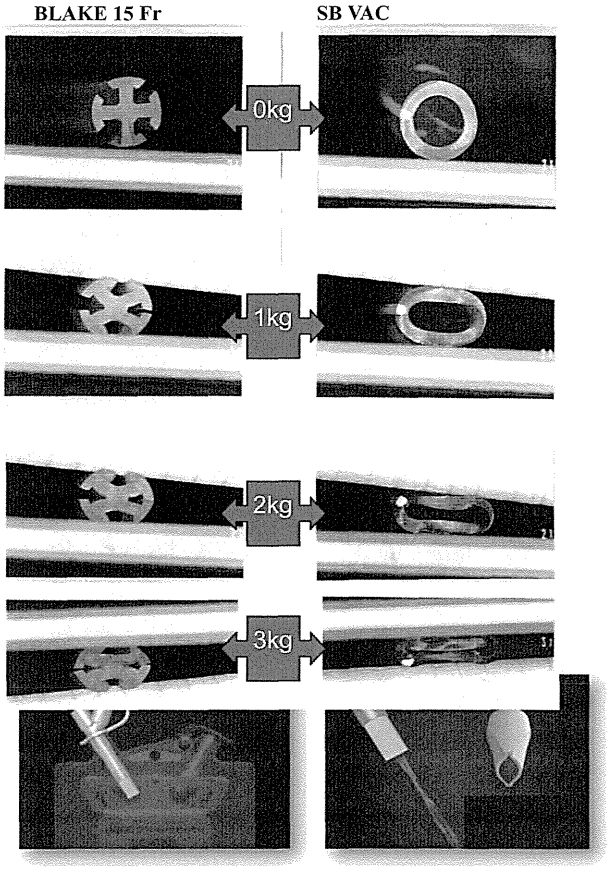

Figure 5 Characteristics of J-VAC drain. Inside the lumen, there are 4 drainage channels. The retrogression prevention valve is adopted in the J-VAC drain (JVD). The diameters of the drain and needle are the same. The leakage from the site of insertion is prevented and retrograde infection is reduced. (The data were provided from Ethicon, Johnson & Johnson; Somerville, NJ.)

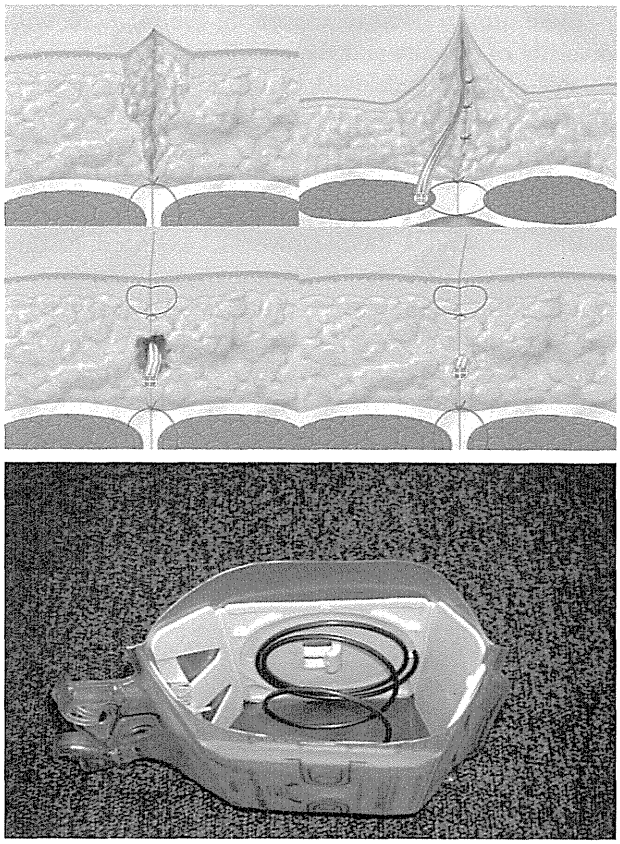

Figure 6 Characteristics of J-VAC drain. The suction bag has an internal spring structure, which allows for constant and sustainable negative pressure. The system not only controls clot and hematoma formation but also reduces the occurrence of delayed wound healing. (The data were provided from Ethicon, Johnson & Johnson; Somerville, NJ.)

subcutaneous tissue closure group, and the non-drain non-subcutaneous tissue closure group revealed that the overall dehiscence rate was 11%; that in the subcutaneous drain without subcutaneous tissue closure group was 14%; that in the non-subcutaneous drain with subcutaneous tissue closure group was 7%; and that in the non-subcutaneous drain and non-subcutaneous tissue closure group was 11%. There were no significant differences among the three groups.[3]

Even if our study cases were limited to those without subcutaneous tissue closure, vertical incision, and subcutaneous fat thickness of more than 3 cm, a low dehiscence rate was still observed (6%, 2/30 cases). Factors such as a small number of obese patients and different methods of disinfection and dressing may have contributed to the low rate of dehiscence in our study.

There are no detailed reports of the relations with quantity of exudate and the effectiveness of the drain. In this study, we showed the differences of exudate volume by subcutaneous fat-tissue closure. Increased accumulation of exudate from postoperative wounds without subcutaneous fat-tissue closure especially in vertical skin incision has a possibility to inhibit wound healing without J-VAC. However, we need further study on whether the difference of accumulation of exudate has an influence on the effectiveness of J-VAC.

In our study, the rate of wound infection was 1.0%, which is lower than in a previous study.[2] Compared to patients in this previous study, our study had fewer obese patients. In the previous study, the overall rate of wound infection was 10%, but all cases had subcutaneous fat thickness greater than 3 cm.

There have been many studies on wound complications (Table 5), including those after cesarean section and other obstetrical surgical procedures. In studies on the use of subcutaneous tissue closure in cesarean section, the frequency of wound complications was lower in those with subcutaneous tissue closure. However, the use of subcutaneous tissue closure in patients with subcutaneous fat thicknesses less than 2 cm did not significantly affect wound complications; therefore, it was not recommended for routine use.[4,12–14]

The use of an open drain has been correlated with an increased risk of wound complications (mainly

Table 5 *Previous reports on wound complications*

Number of subjects	Surgical procedure	Subject	Method	Complication	Results
875[4]	CS	No restriction	Presence of subcutaneous tissue suture	Dehiscence	Subcutaneous tissue suture was effective, but no difference in <2 cm
887[4]	CS	Subcutaneous fat >2 cm	Presence of subcutaneous tissue suture	Dehiscence	Subcutaneous tissue sutures was effective
242[5]	CS	No restriction	Presence of open-drain	Infection	Complications increased by use of the drain Antibiotics not used
76[6]	CS	Subcutaneous fat >2 cm	Only closed-drain or only subcutaneous tissue suture or none	Wound complications	Drain < subcutaneous tissue Suture < none Small number
590[7]	CS	Subcutaneous fat >2 cm	Only closed-drain or only subcutaneous tissue suture or none	Treatment reaquired complications	No difference
118[8]	CS Pfannenstiel	BMI > 32	Presence of drain (without subcutaneous tissue suture)	Infection, dehiscence, redressing	No difference for infection or dehiscence. Redressing was less frequent with the drain
280[9]	CS	Subcutaneous fat >4 cm	Only subcutaneous tissue suture or subcutaneous tissue suture + drain	Wound complications	No difference
222[3]	Technique not specified	Subcutaneous fat >3 cm	Only drain or only subcutaneous tissue suture or none	Wound complications	No difference (strict antibiotics and wound protection protocol)
305[10]	CS	No restriction	Presence of drain	Wound complications	No difference. No need for routine drain use
197[11]	Technique not specified, lower abdominal median incision	Obese patients	Presence of drain (without subcutaneous tissue suture)	Wound complications	No difference (antibiotics used at doctor's discretion) Antibiotic + drain (2%) No drain, no antibiotics (14%)

BMI, body mass index; CS, cesarean section.

retrograde infection).[5] This type of drain creates a route for bacterial infection, and because it is a foreign substance, it could be a source of bacterial bleeding. Furthermore, postoperative antibiotics were not used in that study.

Afterwards, a closed-type drain was used extensively. However, the outcomes were variable, because different studies used different methods (use of antibiotics, subcutaneous tissue closure, deep dermal sutures, insertion site), and the patient characteristics also varied (e.g., thickness of subcutaneous fat). Some studies suggested that the use of a subcutaneous drain was better than subcutaneous suture closure, while others concluded that neither drains nor subcutaneous tissue closure were useful. However, many studies have reported the efficacy of both subcutaneous tissue closure and drains in patients with subcutaneous fat thickness of more than 2 cm. Details of these studies are presented below.[7–11,15] Some studies showed effectiveness of subcutaneous drain even in gynecological surgery.[11]

In patients without subcutaneous tissue closure who were administered antibiotics at a primary doctor's discretion, drain usage did not significantly affect the wound complication rate. However, the frequency of wound complications suited the lower tendency by the combined use of a drain and antibiotics.[11]

In a study comparing the use of closed drains in patients with BMI ≥ 32 who were given antibiotics and did not have subcutaneous tissue closure, there were no significant differences in dehiscence or wound infection rates by the use of drains. There was a reduced number of dressing changes and fevers in the group with drains. Because of antibiotic resistance, the author proposed for a drain to be one of the choices.[8]

Another study[9] analyzed the use of subcutaneous tissue closures versus the use of both subcutaneous tissue closures and drains. There was no significant difference between the groups, and the authors did not recommend the combined use of subcutaneous tissue closures and drains. However, in our study, complications were found in those without subcutaneous tissue closures. Therefore, further studies with more patients are needed to determine whether the use of JVD with subcutaneous tissue closures is necessary.

On the other hand, some reports have identified negative effects of subcutaneous drains. Nabin *et al.*[10] found no significant difference in wound complications with the use of drains. Furthermore, drains were associated with an increased medical cost, longer surgery time, increased use of postoperative analgesic drugs, and increased removal complications (mostly bleeding). Therefore, they did not recommend the use of subcutaneous drains. This study applied antibiotics in all cases, and patients with thin subcutaneous fat were also included. It is possible that those low-risk cases were not indicated for routine insertion of subcutaneous drains. However, another study that included cases with deep subcutaneous fat thickness of more than 2 cm and cases with major complications requiring re-operation (dehiscence, hematoma, and infection) did not find any significant differences in the use of subcutaneous drains, subcutaneous tissue closures, or both.[7] They suggested that it is possible that previous reports included the complications of slight illness, such as small hematoma, without great necessity for medical treatment. They used appropriate antibiotics, and the wound was protected, which could have reduced the frequency of complications requiring further treatment, thus reducing the difference between the drain and subcutaneous tissue closures. Furthermore, a meta-analysis on the efficacy of post-cesarean section subcutaneous drains found that the use of preventive subcutaneous drains did not prevent wound complications.[15]

Compared to previous studies, our study did not identify complications related to drain insertion and removal (i.e., hematomas). In addition, compared with subcutaneous tissue closures, drain insertion probably shortened the length of surgery. The overall complication rate was 3.3% (five cases); of these five cases, only two required further treatment for dehiscence or infection (1%), which is a lower rate than in previous reports. In this study, all cases received both antibiotics and drains, and half of the cases also used subcutaneous fat-tissue closures. Disinfection, shaving, and dressing methods may have played a role in improved wound healing. However, the results of the present study suggest that the use of JVD improved perioperative management of common wounds and reduced the occurrence of complications. Because omitting subcutaneous fat-tissue closures can reduce the length of surgery, JVD is recommended for general surgeries in obstetrics and gynecology.

However, in our study, there was no uniformity on the type of operative procedure and the use of subcutaneous fat-tissue closures, as this was left to the surgeon's discretion. Compared to studies from other countries, there were fewer obese patients in this study, yet there was no restriction on the subjects. Furthermore, there was only a small number of cases with complications; therefore, additional cases are required