limited,[4-14] and each study included fewer than 60 patients, too small a population to allow consensus regarding recommendations for patient selection for fertility-sparing surgery in stage I EOC. This study attempted to determine selection criteria for fertility-sparing surgery in stage I EOC patients on the basis of clinical outcomes for more than 200 stage I EOC patients who underwent fertility-sparing surgery.

PATIENTS AND METHODS

Patients

Between 1985 and 2004, patients with stage I invasive EOC who underwent fertility-sparing surgery in 30 institutions belonging to the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group or who were referred to these hospitals immediately after fertility-sparing surgery performed elsewhere were enrolled onto this study. Patients were eligible if they had stage I, G1, G2, or G3 EOC; if they were treated using fertility-sparing surgery (conservation of the uterus and contralateral ovary and fallopian tube); and if they were ≤ 40 years of age at the time of fertility-sparing surgery. Four patients (stage IB, n = 2; stage IC, n = 2) who showed microscopic metastases in biopsy specimens from the opposite ovary were excluded from this study because of the small number of patients and the insufficient durations of follow-up.

Reassessment of histologic cell type and tumor differentiation was performed in each institution according the WHO criteria before enrollment onto the present study. Histologic differentiation was defined as G1, well differentiated; G2, moderately differentiated; or G3, poorly differentiated. Staging was determined according to the International Federation of Gynecology and Obstetrics (FIGO) classification (1987). In this study, stage IC patients were classified into three subgroups: stage IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule rupture and/or tumor on ovarian surface with negative peritoneal cytology; and IC(1/2), malignant cells in ascites or peritoneal washings. Institutional review board approval was obtained from each institution before initiating this investigation.

Factors for Analysis

Mucinous, serous, endometrioid, and mixed epithelial adenocarcinoma were classified by histologic grade (G1, G2, or G3). Clear cell histology was not graded in this study. We defined G1/2 non-clear cell adenocarcinoma as showing favorable histology.

Stage IA or IC patients with unilateral ovarian involvement were divided into six subgroups to determine patient selection for fertility-sparing surgery, as follows: stage IA and favorable histology, stage IA and clear cell histology, stage IA and G3, stage IC and favorable histology, stage IC and clear cell histology, or stage IC and G3.

We defined lethal recurrence (LR) as recurrence showing lesions outside the remaining ovary, because a considerable number of previous reports[15] have suggested that patients with recurrence exclusively within the remaining ovary show much better prognosis following salvage surgery compared with patients displaying other patterns of recurrence. Outcomes for patients were analyzed using overall survival (OS), recurrence-free survival (RFS), and lethal recurrence–free survival (LRFS). We also investigated reproductive outcomes after fertility-sparing surgery in patients who provided the information.

Statistical Analysis

Statistical analysis of data was performed using the JMP Statistics package (SAS Institute, Cary, NC). Two-sided probability values were calculated throughout and considered to be significant at the level of $P < .05$. Survival estimates were generated using Kaplan-Meier methods. Differences between groups were tested using log-rank testing.

RESULTS

Patient Characteristics

A total of 211 patients with unilateral stage I EOC (stage IA, n = 126; stage IC, n = 85) were entered onto the study. Table 1 summarizes the main characteristics of patients and tumors. Mean patient age was 29 years (range, 14 to 40 years). Median duration of follow-up after excluding patients who died was 78 months from initial fertility-sparing surgery (range, 3 to 270 months).

Surgical Treatments

Of the 211 patients, 23 (10.9%) patients underwent restaging laparotomy because of inadequate staging or cytoreduction at initial surgery. Nine of the 23 patients underwent unilateral ovarian cystectomy at initial surgery (laparoscopy, n = 4; laparotomy, n = 5) and unilateral salpingo-oophorectomy at restaging laparotomy. As a result, 205 patients underwent unilateral salpingo-oophorectomy. The

Table 1. Patient Characteristics (N = 211)

Characteristic	No.	%
Age, years		
Median	29	
Range	14-40	
Parity		
Parous	26	12.3
Nulliparous	185	87.7
FIGO stage		
IA	126	59.7
IC	85	40.3
Substage		
IC(b)	55	26.1
IC(a)	18	8.5
IC(1/2)	12	5.7
Cell type		
Mucinous	126	59.7
Serous	27	12.8
Endometrioid	27	12.8
Clear cell	30	14.2
Mixed epithelial	1	0.5
Histologic differentiation		
Well (G1)	160	75.8
Moderate (G2)	15	7.1
Poor (G3)	6	2.8
Not classified (clear cell)	30	14.2
FIGO stage and histologic differentiation		
IA		
G1	95	47.3
G2	13	6.2
G3	3	1.4
Clear cell	15	7.1
IC		
G1	65	30.8
G2	2	0.9
G3	3	1.4
Clear cell	15	7.1

Abbreviations: G(1/2/3), non-clear cell histology grade (1/2/3); FIGO, International Federation of Gynecology and Obstetrics; IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule ruptured and/or tumor on ovarian surface with negative peritoneal cytology; IC(1/2), malignant cells in ascites or peritoneal washings.

Table 2. Types of Surgery in Initial Treatment

Surgery Type	No. of Patients
Unilateral salpingo-oophorectomy	205
Alone	64
BO	43
OM	16
RLND	5
BO + OM	27
BO + RLND	5
OM + RLND	18
BO + OM + RLND	26
Unknown	1
Unilateral ovarian cystectomy	6
BO	3
RLND	1
BO + OM	1
Unknown	1

Abbreviations: BO, biopsy from the opposite ovary; OM, partial omentectomy; RLND, retroperitoneal lymph node dissection or biopsy.

remaining six patients underwent unilateral ovarian cystectomy at initial laparotomy, not followed by restaging surgery. As for other surgeries, 105 patients underwent biopsy (wedge resection) of the opposite ovary, 88 patients underwent partial omentectomy, and 55 patients underwent retroperitoneal lymph node dissection or biopsies. Table 2 provides details of surgical treatments.

Surgical staging included careful inspection and palpation of peritoneal surfaces with biopsies of any suspect lesions and peritoneal washing cytology. No patients received endometrial curettage during surgery, although most patients had endometrial cytology or biopsy before surgery. If optimal surgical staging required at least omentectomy in addition to unilateral salpingo-oophorectomy, 87 (41.2%) of the 211 patients were optimally staged and 124 (58.8%) were nonoptimally staged. Only 74 (35.1%) patients were optimally staged in one-step surgery.

Adjuvant Chemotherapy

Platinum-based adjuvant chemotherapy was administered to 125 (59.2%) patients, with a mean number of four cycles (range, 1 to 12 cycles). The most common chemotherapy regimens were cisplatin + cyclophosphamide ± doxorubicin (57 of 125; 45.6%) and carboplatin + paclitaxel (46 of 125; 36.8%). Fifteen (7.1%) patients received adjuvant chemotherapy without platinum (including oral medication). The remaining 71 (33.6%) patients received no adjuvant treatment after initial surgery.

Clinical Outcomes

Recurrence was identified during the follow-up period for 18 (8.5%) of 211 patients. Of these 18 patients, five showed recurrence exclusively in the remaining ovary (non-LR; Table 3) and 13 had LR in sites other than the remaining ovary (Table 4). At the end of this investigation, eight patients were alive with no evidence of disease, five patients were alive with disease, and five patients had died of disease. All five patients with non-LR were treated with salvage surgery and showed no evidence of disease.

Stage IA and favorable histology. This subgroup included 108 stage IA patients with favorable histology. Of these, 44 (40.7%) patients received platinum-based adjuvant chemotherapy after surgery, and the 5-year OS, RFS, and LRFS were 100%, 97.8%, and 99.1%, respectively. Three patients with mucinous histology G1 developed LR at 14, 70, and 73 months after fertility-sparing surgery (Table 4). Median duration of follow-up for this group was 79 months.

Stage IA and clear cell histology. This subgroup included 15 stage IA patients with clear cell histology. Of those, nine (60%) patients were treated with platinum-based adjuvant chemotherapy. The 15 patients showed rates of 100% for 5-year OS, RFS, and LRFS. Median duration of follow-up for these patients was 78 months.

Stage IA and G3. One of the three stage IA patients with G3 received platinum-based adjuvant chemotherapy and was alive without recurrence 256 months after fertility-sparing surgery. Two patients without any adjuvant chemotherapy had LR at 25 and 31 months after fertility-sparing surgery (Table 4), although both were alive with disease at the end of this investigation (duration of follow-up, 65 and 90 months).

Stage IC and favorable histology. This subgroup included 67 stage IC patients with favorable histology. Platinum-based adjuvant chemotherapy was administered to 57 (85.1%) patients following surgery. The 5-year OS, RFS, and LRFS were 96.9%, 92.1%, and 95.4%, respectively. As for subgroups of stage IC [IC(b), n = 43; IC(a), n = 14; IC(1/2), n = 10], the 5-year RFS was 92.9%, 91.7%, and 90.0%, respectively. Three (4.5%) of 67 patients developed LR, with one stage IC(b) patient with endometrioid histology G1, one stage IC(b) patient with mucinous histology G1, and one IC(1/2) patient with serous histology G1 developing LR at 20, 8, and 3 months after fertility-sparing surgery, respectively (Table 4). Median duration of follow-up for this group was 76.5 months.

Table 3. Characteristics of Patients With Recurrence in the Residual Ovary Alone (non-lethal recurrence)

Patient No.	Age (years)	Stage	Histologic Type	Grade	Platinum-Based Chemotherapy	Time to Recurrence (months)	Follow-Up After Recurrence (months)	Status
1	18	IA	Mucinous	1	No	83	119	NED
2	26	IA	Serous	1	Yes	52	164	NED
3	26	IC(b)	Endometrioid	1	No	7	45	NED
4	36	IC(b)	Clear cell	Not graded	No	21	124	NED
5	26	IC(a)	Mucinous	1	Yes	43	16	NED

Abbreviations: NED, no evidence of disease; IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule ruptured and/or tumor on ovarian surface with negative peritoneal cytology.

Table 4. Characteristics of Patients Showing Recurrence With Lesions Outside the Residual Ovary (lethal recurrence)

Patient No.	Age (years)	Stage	Histologic Type	Grade	Platinum-Based Chemotherapy	Site of Recurrence	Time to Recurrence (months)	Follow-Up After Recurrence (months)	Status
1	19	IA	Mucinous	1	No	Peritoneum	70	149	NED
2	27	IA	Mucinous	1	No	Lung	73	34	DOD
3	29	IA	Mucinous	1	No	Abdominal wall	14	39	AWD
4	22	IA	Serous	3	No	Residual ovary, ascites	25	231	NED
5	40	IA	Endometrioid	3	No	Para-aortic lymph nodes	31	34	NED
6	15	IC(b)	Mucinous	1	Yes	Peritoneum	8	18	AWD
7	31	IC(b)	Endometrioid	1	Yes	Liver	20	6	DOD
8	29	IC(b)	Clear cell	Not graded	No	Para-aortic lymph nodes	15	86	AWD
9	29	IC(b)	Clear cell	Not graded	Yes	Residual ovary, ascites, peritoneum	11	19	DOD
10	36	IC(b)	Clear cell	Not graded	Yes	Liver	46	8	AWD
11	33	IC(a)	Endometrioid	3	Yes	Not recorded	1	5	DOD
12	26	IC(1/2)	Serous	1	Yes	Peritoneum	3	22	DOD
13	38	IC(1/2)	Clear cell	0	No	Residual ovary, pelvic lymph nodes, peritoneum	21	29	AWD

Abbreviations: NED, no evidence of disease; DOD, died of disease; AWD, alive with disease; IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule ruptured and/or tumor on ovarian surface with negative peritoneal cytology; IC(1/2), malignant cells in ascites or peritoneal washings.

Stage IC and clear cell histology. This subgroup included 15 stage IC patients with clear cell histology. Eleven (73.3%) of these patients were treated with platinum-based adjuvant chemotherapy. LR occurred in two patients with and in two patients without platinum-based adjuvant chemotherapy (Table 4). These 15 patients showed rates of 93.3%, 66.0%, and 72.7% for 5-year OS, RFS, and LRFS. In particular, 5-year RFS of 11 stage IC(b) patients resembled that of the other four stage IC patients (63.6% *v* 75.0%, respectively). Median duration of follow-up for the 14 survivors was 64 months.

Stage IC and G3. All three stage IC patients with G3 were treated using platinum-based chemotherapy after surgery, but one patient developed LR and died of disease 6 months after fertility-sparing surgery. The remaining two patients were alive without recurrence 58 and 230 months after fertility-sparing surgery.

Comparison of Clinical Outcomes Among Subgroups

We compared OS and RFS among the four subgroups except for the two subgroups (stage IA and G3, or stage IC and G3) consisting of only three patients. In terms of OS, no significant differences were seen among the four subgroups. Significant differences in RFS were seen between the following three pairs of subgroups: stage IA favorable histology versus stage IC clear cell histology (97.8% *v* 66.0%; $P < .001$), stage IC favorable histology versus stage IC clear cell histology (92.1% *v* 66.0%; $P = .008$), and stage IA clear cell histology versus stage IC clear cell histology (100% *v* 66.0%; $P = .02$).

Figure 1 shows OS and RFS curves in those with good prognosis (group I: stage IA favorable histology [n = 108]), those with fairly good prognosis (group II: stage IA clear cell histology or stage IC favorable histology [n = 82]), and those with poor prognosis (group III: stage IA G3, stage IC clear cell histology, or stage IC G3 [n = 21]). No significant differences in OS were seen between groups I and II ($P = .21$) or between groups II and III ($P = .29$), whereas significant differences were identified between groups I and III ($P = .02$). No significant differences in RFS were apparent between groups I and II ($P = .65$), but significant differences were noted between groups I and III ($P < .001$) and between groups II and III ($P < .001$).

Reproductive Outcomes

After fertility-sparing surgery with or without adjuvant chemotherapy, 182 (96.8%) of 188 patients who gave information on menstruation had almost the same cycle of menstruation as before treatment. Six (5.0%) of 121 patients who received platinum-based adjuvant chemotherapy showed continued secondary amenorrhea for 6, 48, 66, 72, 172, and 224 months following two to six cycles of chemotherapy (median, four cycles).

Of the 195 patients who gave reproductive outcomes at the end of the investigation, 55 (28.5%) patients achieved 76 pregnancies and 53 gave birth to 66 healthy children after fertility-sparing surgery. Five (9.1%) of 55 patients had received some kind of infertility treatment before pregnancy. These patients and their babies showed no clinical problems during the perinatal period. Four (9.4%) of 53 patients who gave birth to children underwent completion surgery, including hysterectomy and contralateral salpingo-oophorectomy, after childbearing.

Forty-five (53.6%) of 84 patients who were nulliparous at fertility-sparing surgery and married at the end of the follow-up period had achieved 65 pregnancies, and 43 had given birth to 56 healthy children during follow-up (mean follow-up, 8.8 years). Of the 84 patients, the remaining 39 patients had not conceived during follow-up (mean follow-up, 7.2 years), and mean age was 37 years (range, 25 to 54 years) at the end of the investigation.

DISCUSSION

In this series, recurrence rate among the 211 stage I EOC patients after fertility-sparing surgery was 8.5% (18 of 211), falling within the 5.4% to 30.3% reported previously.[5,6,10,12,14] Of the 18 patients with recurrence, five (2.4%) patients showing recurrence exclusively in the residual ovary achieved no evidence of disease. According to data from five studies[5,6,10,12,14] that investigated relationships between sites of recurrence and clinical outcomes, eight of 10 patients with recurrence limited to the residual ovary achieved no evidence of disease following salvage therapy, whereas only three of 21 patients with recurrence at

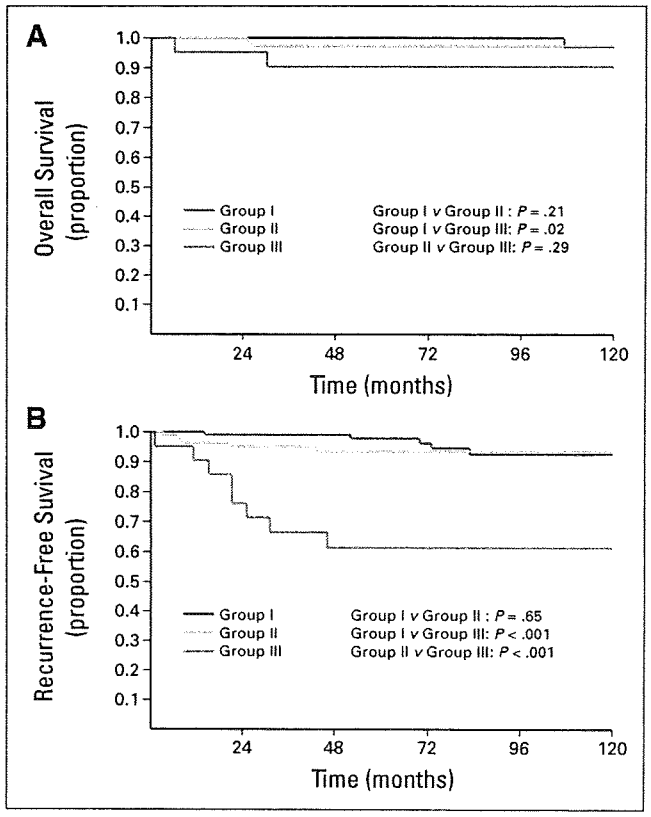

Fig 1. (A) Overall survival curves for patients with good prognosis (group I), fairly good prognosis (group II), and poor prognosis (group III). Group I: stage IA and favorable histology; group II: stage IA and clear cell histology, or stage IC and favorable histology; group III: stage IA and clear cell histology grade 3 (G3), stage IC and clear cell histology, or stage IC and G3. (B) Recurrence-free survival curves for groups I, II, and III.

extra-ovarian sites achieved no evidence of disease. We thus evaluated LRFS in addition to OS and RFS in this study.

The 108 stage IA patients with favorable histology showed a 5-year RFS of 97.8% and a 5-year LRFS of 99.1% (5-year recurrence rate, 2.2%; 5-year LR rate, 0.9%), although only 40.7% of these patients received platinum-based adjuvant chemotherapy after surgery. Stage IA patients with favorable histology were always included in selection criteria for fertility-sparing surgery in previous reports and in various guidelines.[1-14] The recurrence rate for stage IA patients with favorable histology in four previous reports[5,10,12,14] was 0% to 22.2% during follow-up. Our data confirm fertility-sparing surgery as a safe treatment option for stage IA patients with favorable histology, even when fertility-sparing surgery is not followed by adjuvant chemotherapy.

In this study, 15 stage IA patients with clear cell histology showed no recurrence, with lymph node biopsy or dissection performed in six (40%) patients and adjuvant platinum-based chemotherapy given to nine (60%) patients. Our data correspond with that in a recent report by Kajiyama et al[16] showing no recurrence in four stage IA patients with clear cell histology who had undergone fertility-sparing surgery. Other investigations,[10,12,14] however, have reported three recurrences among eight stage IA patients with clear cell histology after fertility-sparing surgery. These data suggest that stage IA patients with clear cell histology may be candidates for fertility-sparing surgery, including optimal staging followed by adjuvant chemotherapy.

In our series, only one of three stage IA patients with G3 survived for 5 years without recurrence. The recurrence rate for the 17 stage IA patients with G3 from six investigations[5,7,10-12,14] who underwent fertility-sparing surgery was 35.3% (6 of 17), although some reports classified clear cell histology into G3. These data suggest that fertility-sparing surgery cannot be recommended for stage IA patients with G3.

The 67 stage IC patients with favorable histology had a 5-year RFS of 92.1% and a 5-year LRFS of 95.5%. Outcomes seem to be better in our study compared with the recurrence rate of 12.8% (5 of 39) in previous studies.[7,10-12,14] Platinum-based adjuvant chemotherapy was more frequently given to this group compared with the stage IA and favorable histology group (85.1% *v* 40.7%; $P < .001$). In our series, no significant difference in 5-year RFS was seen among 43 IC(b) patients, 14 IC(a) patients, or 10 IC(1/2) patients with values of 92.9%, 91.7%, and 90.0%, respectively. Our data suggest that stage IC patients with favorable histology in the unilateral ovary can be candidates for fertility-sparing surgery, including optimal staging followed by adjuvant chemotherapy.

Our series included 15 stage IC patients with clear cell histology. These patients showed a 5-year RFS of 66.0% and a 5-year LRFS of 72.7%, even when 11 (73.3%) patients were treated with platinum-based adjuvant chemotherapy. Kajiyama[16] reported that one stage IC(2) patient among the six stage IC patients with clear cell histology experienced relapse and died of the disease. Five-year RFS was 63.6% for 11 IC(b) patients, 100% for two IC(a) patients, and 50% for two IC(1/2) patients. These data suggest that stage IC patients with clear cell histology cannot be candidates for fertility-sparing surgery.

Our series included three stage IC patients with G3. One patient developed LR and died of the disease 6 months after fertility-sparing surgery, although all three patients had been treated with platinum-based adjuvant chemotherapy. In previous reports,[10-14] four of nine stage IC patients with G3 who underwent fertility-sparing surgery displayed recurrence. These data suggest that fertility-sparing surgery cannot be recommended for stage IC patients with G3.

In addition to the study patients, during the study period, we managed four patients with unilateral stage I EOC treated with fertility-sparing surgery elsewhere, who were referred to these hospitals for treatment of lethal recurrent disease and died of the disease. These four patients included one stage IA patient with clear cell histology, one stage IA patient with G3, and two stage IC patients with G3. Clinical outcomes for these patients support our recommendations regarding fertility-sparing surgery for unilateral stage I EOC.

In our series, 5% of patients with platinum-based adjuvant chemotherapy developed secondary amenorrhea and infertility, suggesting that we should not administer adjuvant chemotherapy to patients with stage IA and favorable histology without serious consideration. As for the reproductive outcome, we confirmed that most married but nulliparous EOC patients undergoing fertility-sparing surgery can give birth to children within several years after fertility-sparing surgery.

In conclusion, this study confirmed that stage IA EOC patients with favorable histology can be safely treated with fertility-sparing surgery not followed by platinum-based adjuvant chemotherapy. We would thus propose that fertility-sparing surgery be considered

Table 5. Recommendation for Fertility-Sparing Surgery in Young Patients With Unilateral Stage I Ovarian Cancer

Stage	Histology/Grade		
	FH	CCH	G3
1A	Offer FSS	Consider FSS + CT	No FSS
1C	Consider FSS + CT	No FSS	No FSS

Abbreviations: FH, favorable histology (mucinous, serous, endometrioid, or mixed histology and grade 1 or 2); CCH, clear cell histology; G3, clear cell histology grade 3; FSS, fertility-sparing surgery; CT, adjuvant chemotherapy.

for stage IA EOC patients with clear cell histology and for stage IC EOC patients with unilateral ovarian involvement and favorable histology, under conditions of performing complete staging surgery and platinum-based adjuvant chemotherapy (Table 5). Conversely, fertility-sparing surgery cannot be recommended for patients with stage IA with G3 histology or stage IC with clear cell or G3 histology. Theoretically, a randomized controlled trial may be needed to compare conservative surgery with radical surgery for young patients with EOC to achieve high-quality evidence. However, such trials may not be ethically feasible. Confirming the decision of patient criteria for selection in a phase II trial would be appropriate.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

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Is randomized trial of neoadjuvant chemotherapy of ovarian cancer necessary?

To the Editor,

I have read the interesting paper of Onda et al. [1] in the January issue. There is a well concerted effort to see the efficacy of neoadjuvant chemotherapy in advanced ovarian cancer by large randomized trials. Two of them are EORTC protocol 55971 and Japan Clinical Oncology Group Study JCOG0602. With the high response rate of carboplatin-paclitaxel, benefit of neoadjuvant chemotherapy must be reaching a higher number of sufferers now. I have noticed an interesting finding of Schwartz (2008) [2] which I think is very correct. If 23% of stage III and 8% of stage IV are amenable to satisfactory cytoreduction (Schwartz 2008) and anecdotal about 70% ovarian cancer is in the advanced stage how come primary cytoreduction can compete with neoadjuvant chemotherapy as is done in RCTs. This is because a number of patients get fully treated in the neoadjuvant arm and is clearly much above those in the primary cytoreduction arm in practice. How can they be compared? Universality of neoadjuvant arm due to 90% response rate of carbo-pacli should negate any such competition and comparison. A much greater number of such ovarian cancers must be treated now. At least my experience is like this. Many more women must be living for many more years. The total sum of life year saved by neoadjuvant is important now and need be calculated.

Conflict of interest statement
Author has no conflict of interest to declare.

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A phase III randomized trial comparing neoadjuvant chemotherapy and upfront debulking surgery is indispensable as a basis for changing the standard treatment of advanced Müllerian cancer

To the Editor,

We appreciate the question raised by Dr. Chinmoy K. Bose regarding our ongoing phase III study [1], which follows on from a feasibility study of neoadjuvant chemotherapy (NAC) published in a recent issue of this journal [2]. We would like to reply by stating our opinion for the necessity of randomized trials that compare NAC-setting treatment (NACT) and primary debulking surgery followed by chemotherapy (PDS-CT).

As Dr. Bose mentioned, considering the high response rate to TC chemotherapy (paclitaxel and carboplatin) and the disappointingly low rate of successful cytoreduction in primary debulking surgery, NACT is expected to improve the dismal prognosis of advanced Müllerian cancer patients. We had also expected a favorable treatment outcome using NACT, and thus conducted the Japan Clinical Oncology Group (JCOG) 0206 study. In this study, we confirmed the promising treatment outcome and the safety of NACT. However, these results were insufficient to prove the superiority of NACT compared to PDS-CT. To date, several studies have compared the results of treatment with either NACT or PDS-CT for advanced ovarian cancer (Table 1). With the exception of the studies by Jacob et al. [3], Kuhn et al. [4], and Vrščaj and Rakar [5], NACT was administered to elderly patients, patients who had more advanced disease or had a lower performance status. Although the selection of treatment in these studies was highly biased, and as such was unfavorable to NACT, most of the studies yielded comparable results using NACT that were not significantly different to those obtained using PDS-CT. Moreover, in a non-randomized phase II study, Kuhn et al. reported a better outcome for the patients receiving NACT compared to those receiving PDS-CT. We thus consider that NACT is potentially promising, although on the basis of the currently available data we are as yet unable to conclude that NACT is superior to PDS-CT. Indeed, the possibility remains that NACT is rather inferior compared to PDS-CT.

In general, in order to change the standard treatment for advanced Müllerian cancer, it is necessary to demonstrate the superiority of NACT in treatment outcome or to show the non-inferiority of NACT in terms of treatment outcome and lower toxicity compared to PDS-CT. The most reliable and quickest way to demonstrate the superiority or non-inferiority of NACT is, we believe, to conduct a randomized phase III study comparing NACT and PDS-CT. Until we are able to obtain conclusive evidence that NACT is superior to PDS-CT as a standard treatment for advanced Müllerian cancer, we should refrain from selecting an easy way to administer NACT for all cases of advanced Müllerian cancer.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

Table 1
Comparison of treatment outcomes between NACT and PDS-CT.

Author	Treatment	Number	Median survival		5-year survival	
			Time (months)	Statistical difference	Rate	Statistical difference
Jacob et al. [3]	PDS-CT	18	18			
	NACT	22	16	NS		
Onnis et al. [6]	PDS-CT	284			21%	
	NACT	88			19%	NS
Schwartz et al. [7]	PDS-CT	206	26			
	NACT	59	13	NS		
Kayikçioğlu et al. [8]	PDS-CT	158	38		24%	
	NACT	45	34	NS	30%	NS
Kuhn et al. [4]	PDS-CT	32	23			
	NACT	31	42	$p=0.007$		
Vrščaj and Rakar [5]	PDS-CT	55	26			
	NACT	20	25	NS		
Loizzi et al. [9]	PDS-CT	30	40			
	NACT	30	32	NS		
Hegazy et al. [10]	PDS-CT	32	28			
	NACT	27	25	NS		
Lee et al. [11]	PDS-CT	22	55			
	NACT	18	53	NS		
Everett et al. [12]	PDS-CT	102	42			
	NACT	98	33	NS		
Inciura et al. [13]	PDS-CT	361	25			
	NACT	213	24	NS		
Hou et al. [14]	PDS-CT	109	47			
	NACT	63	46	NS		

PDS-CT: primary debulking surgery followed by chemotherapy, NACT: neoadjuvant chemotherapy-setting treatment, NS: not significant.

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The Optimal Debulking after Neoadjuvant Chemotherapy in Ovarian Cancer: Proposal Based on Interval Look During Upfront Surgery Setting Treatment

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Objective: The optimal goal of interval debulking surgery (IDS) following neoadjuvant chemotherapy (NAC) remains undefined. The aim of this study was to determine the optimal goal of IDS following NAC on the basis of long-term survival by the disease status at the end of interval look surgery (ILS) or IDS during the treatment in the setting of upfront primary debulking surgery (PDS).

Methods: From January 1986 through December 2000, we performed treatment in the setting of upfront PDS in 128 patients with Stage III/IV epithelial ovarian cancer. Sixty-six patients with residual disease (RD) at PDS underwent interval surgery (IS) such as ILS or IDS; 4 patients after two cycles of chemotherapy and 62 after three or more cycles. We investigated how disease status at the end of IS was associated with overall survival (OS).

Results: The 5-year OS rates for no, minimal and gross RD were not available ($n = 0$), 67% ($n = 3$) and 0% ($n = 1$) after two cycles, and 47% ($n = 42$), 0% ($n = 18$) and 0% ($n = 2$) after three or more cycles, respectively. No visible tumors at the end of IS after three or more cycles of chemotherapy were necessary for 5-year survival.

Conclusions: If the optimal goal of IDS is defined as the surgery that is expected to result in long-term survival in the NAC setting treatment, our data on the assessment of peritoneal findings during the upfront PDS setting treatment suggest that only complete resection with no RD could be the optimal goal of IDS in the NAC setting treatment.

Key words: ovarian cancer – neoadjuvant therapy – gynecol-surg – chemo-gynecology

INTRODUCTION

Primary debulking surgery (PDS) followed by chemotherapy is a standard treatment for ovarian cancer. For patients with advanced ovarian cancer, the goal of PDS is optimal cytoreduction, usually defined as surgery with residual disease (RD) <1 or <2 cm in diameter. Proportion of patients who achieved optimal surgery or size of RD is one of the important prognostic factors for the patients with advanced ovarian cancer (1–4). Unfortunately, optimal cytoreduction for advanced ovarian cancer is achieved in only 30–60% of the patients at most institutions (5,6). One reason for this low rate is that patients with advanced ovarian cancer are often poor candidates for aggressive surgery because of low performance status (PS) caused by massive ascites, pleural effusion and large abdominal tumors. Another reason is that some patients have unresectable tumors at the time of primary surgery.

Thus, because of recent advances in chemotherapy, neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) and further chemotherapy has become an alternative treatment for patients with low PS and those with apparently unresectable tumors evaluated with computed

tomography (CT) or laparoscopy. Several retrospective studies revealed comparable results by the NAC setting treatments with standard treatment (7–9), and a few prospective Phase II (10) or feasibility study (11,12) revealed promising results by NAC setting treatment. Taking into account these favorable outcomes of NAC setting treatment, several prospective clinical trials are now under way to compare this treatment with the standard treatment for advanced ovarian cancer, not only in patients with low PS or unresectable tumors (13,14). Most previous studies have emphasized that the greatest advantage of the treatment in the setting of an NAC is a higher rate of optimal cytoreduction at IDS (7,9,10). These studies used the same definition of optimal cytoreduction at IDS as that at PDS. At the time of PDS, optimal cytoreduction indicates an optimal goal of surgery that lengthens survival. However, there is limited information on the survival of patients in relation to the size of RD after IDS. Thus, the appropriate definition of 'optimal cytoreduction' at the time of IDS in the setting of NAC is undetermined.

Since 1986, we have performed interval look surgery (ILS) for patients who have minimal RD (<2 cm in diameter) at PDS or IDS for patients who have gross RD (≥2 cm in diameter) at PDS after two to six cycles (mostly three or four cycles) of chemotherapy. We investigated how peritoneal findings at the end of interval surgery (IS) are associated with the overall survival (OS) of patients. These associations should help us to clarify the optimal goal of IDS in the setting of NAC for advanced ovarian cancer.

PATIENTS AND METHODS

Patients

From January 1986 through December 2000, we treated 230 patients with epithelial ovarian cancer, including 128 patients with Stage III–IV disease, at the Department of Obstetrics and Gynecology, University of Tokyo Hospital. According to the International Federation of Gynecology and Obstetrics (FIGO) staging, disease was classified as Stage IIIB in 14 patients, Stage IIIC in 89 patients and Stage IV in 25 patients. Histologic type was serous in 94 patients, clear cell in 18 patients, endometrioid in 6 patients, mucinous in 5 patients, transitional cell in 2 patients, mixed epithelial in 2 patients and undifferentiated in 1 patient. Median age at the time of PDS was 54 years, with a range of 29–78 years. Median follow-up period after PDS, excluding patients who died, was 94 months, with a range of 8–201 months. All but two surviving patients were followed up for >5 years.

Our standard surgical treatment for advanced ovarian cancer at the time of PDS consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic or total omentectomy, and debulking of peritoneal tumor masses with maximum efforts. Patients with no or minimal RD (<2 cm in diameter) also underwent systematic retroperitoneal lymphadenectomy, except for patients with severe medical complications, low PS or long operation time. Retroperitoneal lymphadenectomy included both the pelvic and aortic lymph nodes.

In principle, our primary management for ovarian cancer was performed as follows according to the outcome of PDS: (i) patients with no RD received six cycles of chemotherapy and underwent no additional surgery, (ii) patients with minimal RD (<2 cm in diameter) received three or four cycles of chemotherapy followed by ILS and two to four cycles of additional chemotherapy, (iii) patients with gross RD (≥2 cm in diameter) received two to four cycles of chemotherapy until a favorable response was obtained and underwent IDS followed by four to five cycles of additional chemotherapy.

Cisplatin-based regimens, such as CAP or TC, were used for post-operative chemotherapy. From 1986 through 1997, we used the CAP regimen, consisting of 400–600 mg/m^2 of cyclophosphamide, 30–40 mg/m^2 of doxorubicin and 50–75 mg/m^2 of cisplatin. Thereafter, we used the TC regimen consisting of paclitaxel (175 mg/m^2 infused over 3 h) and an area under the curve 6 of carboplatin.

Statistical Methods

OS was measured from the day of starting primary treatment. The survival curves were determined with the Kaplan–Meier product-limit method. Differences in survival were analyzed with the log-rank test and Cox proportional-hazard regression model using the SPSS program ver. 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Survival of all Patients in Relation to the Size of RD at PDS

In 128 patients with Stage III or IV ovarian cancer, complete resection of all visible tumors was achieved in 37 patients (28.9%), minimal RD remained in 52 patients (40.6%) and gross RD remained in 39 patients (30.5%). Figure 1 shows the OS of all 128 patients with Stage III/IV disease in relation to the largest size of RD at PDS. Median OSs and 5-year OS rates of the above three groups were 112 months and 65%, 50 months and 40%, and 22 months and 13%. The difference in OS among the three groups was statistically significant ($P < 0.0001$ with log-rank test). In particular, the difference in OS between patients with minimal RD and gross RD was more significant than that between patients with no RD and minimal RD ($P < 0001$ vs. $P = 0.02$). Hazard ratio and 95% confidence interval (CI) for patients with minimal RD and gross RD against patients with no RD were 1.92 (1.08–3.42) and 5.43 (2.98–9.89), respectively.

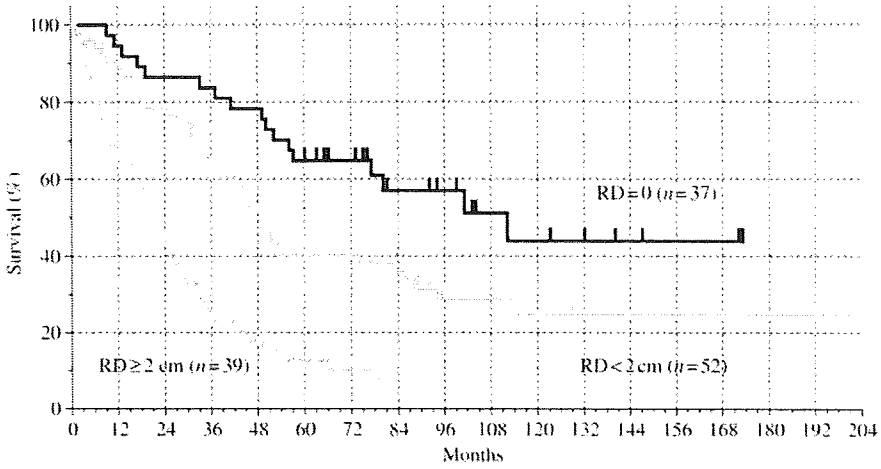

Figure 1. Overall survival of the patients with Stage III/IV ovarian cancer according to the size of largest RD at the time of PDS. RD, residual disease; PDS, primary debulking surgery.

Performance of IS

For Patients with Minimal RD at PDS

Of the 52 patients with minimal RD at PDS, 29 underwent ILS after three or four cycles of post-operative chemotherapy. Nine patients underwent ILS after five or six cycles of chemotherapy. The remaining 14 patients did not undergo ILS due to the following reasons: progressive disease in 2 patients, unfavorable response in 2 patients, entry to clinical trial in 4 patients, patient refusal in 1 patient, medical complications in 4 patients and unknown reason in 1 patient.

For Patients with Gross RD at PDS

Of 39 patients with gross RD at PDS, 28 underwent IDS after two to six cycles of post-operative chemotherapy. Four patients underwent IDS after two cycles of chemotherapy because of early partial responses, 20 patients underwent IDS after three or four cycles of chemotherapy and 4 patients underwent IDS after six cycles of chemotherapy. The remaining 11 patients did not undergo IDS because of progressive disease in 9 patients and medical complications in 2 patients.

RD at the end of IS and OS

IDS after Two Cycles of Chemotherapy

Four patients underwent IDS after two cycles of chemotherapy. Three patients had minimal RD and one patient had gross RD at the end of IDS. Median OSs and 5-year OS rates were 66 months and 67% in patients with minimal RD and 8 months and 0% in a patient with gross RD. The mean number of chemotherapy cycles after IDS was 5.3 (range, 3–6) for patients with minimal RD and 1 (range, 1–1) for a patient with gross RD. Two patients with minimal RD after IDS survived >5 years.

ILS and IDS after Three or More Cycles of Chemotherapy

Thirty-eight patients underwent ILS after three or more cycles of chemotherapy. At the end of ILS, 32 patients had no RD, 5 had minimal RD and 1 had gross RD. Median OSs and 5-year OS rates were 83 months and 55% in patients with no RD, 16 months and 0% in patients with minimal RD and 11 months and 0% in a patient with gross RD. The mean number of chemotherapy cycles after ILS was 2.8 (range, 0–5) for patients with no RD, 2.8 (range, 0–6) for patients with minimal RD and 2 (range, 2–2) for a patient with gross RD.

Twenty-four patients underwent IDS after three or more cycles of chemotherapy. At the end of IDS, 10 patients had no RD, 13 had minimal RD and 1 had gross RD. Median OSs and 5-year OS rates were 28 months and 20% in patients with no RD, 23 months and 0% in patients with minimal RD and 8 months and 0% in a patient with gross RD. The mean number of chemotherapy cycles after IDS was 3.4 (range, 0–5) for patients with no RD, 4.1 (range, 2–7) for patients with minimal RD and 1 (range, 1–1) for a patient with gross RD.

Overall, 42 patients had no RD, 18 had minimal RD and 2 had gross RD at the end of IS such as ILS and IDS after three or more cycles of chemotherapy. Median OSs and 5-year OS rates were 53 months and 47% in patients with no RD, 23 months and 0% in patients with minimal RD and 11 months and 0% in patients with gross RD. The difference in OS among the three groups was statistically significant ($P < 0.0001$ with the log-rank test, Fig. 2). The difference in OS between patients with no RD and minimal RD was much more significant than that between patients with minimal RD and gross RD ($P < 0.0001$ vs. $P = 0.04$). None of these patients with RD at the end of IS after three or more cycles of chemotherapy survived >5 years. Hazard ratio and 95% CI for patients with minimal RD and gross RD against

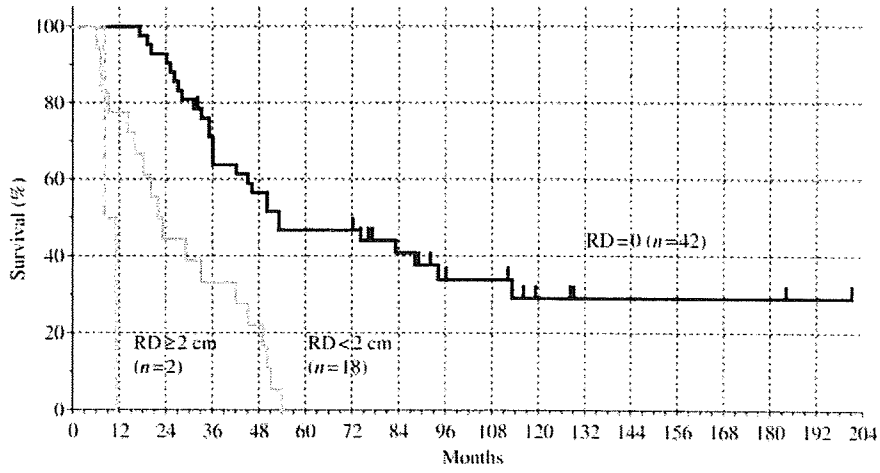

Figure 2. Overall survival of the patients who underwent IS after three or more cycles of chemotherapy according to the size of largest RD at the end of IS. IS, interval surgery.

patients with no RD were 3.99 (2.11–7.55) and 32.78 (5.67–189.55), respectively.

DISCUSSION

NAC setting treatment for advanced ovarian cancer has lately attracted much attention and randomized controlled trials are now under way comparing the outcome with the treatment in the setting of upfront PDS (13,14). However, because of the paucity of the data, optimal goal of IDS in the NAC setting treatment has not yet determined. For our management of advanced ovarian cancer, we performed ILS for patients with minimal RD to assess the peritoneal findings mainly after three to four cycles of chemotherapy separate from IDS for patients with gross RD. Although our data are not based on the treatment results of NAC setting treatment, we thought that the disease status at the time of IDS or ILS in patients who had good outcomes would be useful for determining the optimal goal of IDS following NAC from the standpoint of cell biology. Similar assessments may be possible by the data of two large Phase III studies of IDS after suboptimal PDS for advanced ovarian cancer (15,16). However, it is regrettable that these studied did not address the issue.

Patients with Stage III/IV disease in our series had relatively good outcomes: a median OS of 46 months and a 5-year OS rate of 39%. We used RD < 2 cm in diameter as the definition of optimal cytoreduction at PDS because our study is a retrospective analysis of patients treated from 1980s. Among these patients, those with no RD had good outcomes: a median OS of 112 and a 5-year OS rate of 65%, whereas patients with minimal RD also had good outcomes: a median OS of 50 months and a 5-year OS rate of 40%. However, patients with gross RD had much poorer outcomes: a median OS of 22 months and a 5-year OS rate of 13% (Fig. 1). Patients who underwent optimal debulking at PDS survived significantly longer than those who underwent suboptimal debulking at PDS (median OS of 74 vs. 22 months, 5-year OS rate of 51% vs. 13%, $P < 0.0001$ with the log-rank test). Hazard ratio of the patients with suboptimal debulking against optimal debulking was 3.65 (95% CI: 2.31–5.71). In agreement with previous reports, our present study confirmed that the optimal goal at PDS is cytoreduction with no or minimal RD.

To determine the optimal goal of IDS following NAC, OS in relation to the size of RD after surgery should be known. However, at present, we have little information on the relation between the outcome of IDS following NAC and long-term survival. A recent analysis of NAC and IDS by Le et al. (17) has found that progression-free survival was significantly improved in patients with complete resection at IDS and did not differ significantly among patients with various sizes of macroscopic RD (<1, 1–2 or >2 cm). However, Le et al. could not find significant improvement in OS of patients with complete resection, likely because of the small number of patients in each group and the short median follow-up time of 19 months. In the present study, we tried to determine the optimal goal of IDS following NAC using peritoneal findings at corresponding timing in patients undergoing treatment in the setting of upfront PDS and having fairly good outcomes. The optimal goal of IDS following NAC should be a favorable status that leads to good long-term survival. The present study suggests that no RD at the end of IS after three or more cycles of chemotherapy can lead to fairly good survival. Although the survivals are not identical following ILS or IDS, combined survival of the patients with no RD at ILS or IDS is comparable to that achieved with minimal RD at PDS in the setting of upfront PDS (median OS of 53 and 50 months and 5-year OS rate of 47% and 40%, Figs 2 and 1, respectively). The survival of the patients with no RD was much better than the patients with any RD, especially in 5-year OS rate (median OS of 53 vs. 22 months, 5-year OS rate of 47% vs. 0%, $P < 0.0001$

with the log-rank test). Hazard ratio of the patients with any RD against no RD was 4.26 (95% CI: 2.27–7.96). However, if IDS is performed after good response to two cycles of chemotherapy, even patients with minimal RD may be expected to obtain good long-term survival (median OS of 66 months and 5-year OS rate of 67%).

In the setting of upfront PDS, RD is chemo-naive and will be exposed to at least six cycles of post-operative chemotherapy. However, in the treatment of NAC and IDS, RD is not chemo-naive, and the number of chemotherapy cycles given after IDS is limited (usually three to four cycles), suggesting that residual cancer cells are less likely to disappear completely following IDS than following PDS. In our series, patients with minimal RD at the end of IS after three to six cycles of chemotherapy received, an average, 3.9 cycles of additional chemotherapy and a total of 8.0 cycles of chemotherapy, which are slightly more than those received by patients with no RD at the end of IS (2.9 and 7.1 cycles, respectively). Previous reports have shown that additional cycles of chemotherapy after six cycles do not improve survival (18,19). Thus, the OS might not improve with an increased number of chemotherapy cycles in patients with minimal RD at the end of IS.

Because of long study period and retrospective nature of the study, we used the definition of <2 cm as minimal RD at IDS. Thus, there may be a room to discuss about survival of patients with much smaller RD. However, our result showed that none of the 20 patients with any RD at the end of IS after three or more cycles of chemotherapy survived >5 years. Because we tried to define the optimal surgery mainly by the condition that leads patients to long-term survival, the results may be similar even if we could divide the patients at smaller RD such as <0.5 or <1 cm.

From our results, we believe that OS of patients with no RD after IDS in the setting of NAC is comparable to that of patients with minimal RD after PDS and is slightly inferior to that of patients with no RD after PDS in the setting of upfront PDS. Therefore, to obtain better OS by the NAC setting treatment compared with standard treatment, complete resection with no RD at IDS by the NAC setting treatment should be higher than the rate of cytoreduction with no or minimal RD at PDS by the upfront PDS setting treatment. Recent presentation of the results of Phase III study conducted by European Organization for Research and Treatment of Cancer (13) at the meeting of International Gynecologic Cancer Society (Bangkok, Thailand, October 2008) showed that OSs for patients treated with PDS or NAC setting treatment are similar (29 vs. 30 months), irrespective of much higher rate of achieving residual tumor <1 cm in IDS compared with PDS (83% vs. 48%). These results may support our result that definition of the optimal surgery for PDS and IDS should be different.

In conclusion, on the basis of long-term follow-up data in patients undergoing upfront PDS setting treatment and having assessment of peritoneal findings during chemotherapy, we propose that the optimal goal of the IDS following three or more cycles of NAC is only complete resection of all visible tumors. However, our study was a retrospective analysis and included only a small number of patients. The definition of optimal cytoreduction at PDS has been established on the basis of long-term clinical data. Similarly, accumulation of data regarding IDS outcomes and OSs in the setting of NAC may be necessary for wide spread acceptance of our proposal.

Conflict of interest statement

None declared.

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Clinical Trial Note

A Phase III Trial of Paclitaxel plus Carboplatin Versus Paclitaxel plus Cisplatin in Stage IVB, Persistent or Recurrent Cervical Cancer: Gynecologic Cancer Study Group/Japan Clinical Oncology Group Study (JCOG0505)

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A randomized controlled trial has been started in Japan to compare the utility of palliative chemotherapy containing paclitaxel and carboplatin (TC) with paclitaxel and cisplatin (TP) as a standard treatment for patients with the newly diagnosed Stage IVB, persistent or recurrent cervical cancer who are not amenable to curative treatment with local therapy. This trial was designed to evaluate the non-inferiority of TC as measured by the number of hospitalized days as an indicator of quality of life (QOL) when compared with TP combination therapy. The primary endpoint is overall survival. Secondary endpoints are progression-free survival, response rates, adverse events, severe adverse events and the proportion of non-hospitalization periods compared with planned treatment periods.

Key words: *cervical cancer – palliative chemotherapy – recurrent – persistent – Stage IVB – cisplatin – carboplatin – paclitaxel*

PROTOCOL DIGEST OF THE JCOG0505

Trial Backgrounds

The prognosis of patients with metastatic, recurrent or persistent cervical cancer who are not amenable to curative treatment with surgery and/or radiation therapy is still poor. Therefore, systemic chemotherapy is currently regarded as a key modality that should be further developed. The importance of combination chemotherapy as well as a single active or new agent is well recognized in the results of the Gynecologic Oncology Group (GOG) study. In a previous GOG study, single agent cisplatin was compared with cisplatin plus paclitaxel (TP) in patients with squamous cell cervical cancer. The combination therapy resulted in a higher response rate and longer median progression-free survival, but the overall survival between the two groups was similar (1). In another study that showed a survival benefit with multiagent therapy, single agent cisplatin was compared with cisplatin plus topotecan. However, this combination therapy had significantly higher toxicity (e.g. 70% versus 1.4% Grade 3 or 4 neutropenia) (2). A recent study reported promising results with TP combination therapy. In this study, incurable cervical cancer patients, including patients with adenocarcinoma or adenosquamous cell carcinoma, were randomly assigned to receive TP, cisplatin plus topotecan, or two other cisplatin-containing combinations. TP showed superiority over the other combination therapies in overall survival (3). Therefore, the present standard regimen in

Europe and the USA is TP combination therapy. However, we have also reported a promising and feasible combination chemotherapy consisting of paclitaxel and carboplatin (TC) in a Phase II study (4). Although as single agents, carboplatin has a lower response rate than cisplatin, the reduced nephrotoxicity of carboplatin does not require hydration, enabling a 3 h administration of paclitaxel in this combination therapy. Thus, TC combination has been available in the outpatient setting. Recently, non-squamous cell cervical cancer has been increasing and treating this disease is a significant priority. Our Phase II study targeted not only patients with squamous cell cervical cancer but also those with non-squamous cervical cancer. We have started a Phase III trial to evaluate the benefit and reduced toxicity of TC for incurable patients with either squamous or non-squamous cell cervical cancer.

The study protocol was designed by the Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG), approved by the Protocol Review Committee of the JCOG on 12 January 2006 and activated on 21 February 2006. This trial was registered at the UMIN Clinical Trials Registry as C000000335 (http://www.umin.ac.jp/ctr/index.htm).

Purpose

This prospective study aims to evaluate the clinical benefits of TC compared with TP for patients with Stage IVB, persistent or recurrent cervical cancer.

Study Setting

This study is a multi-institutional (30 specialized institutions), randomized controlled trial.

Resources

The study is supported in part by Health and Labour Science Research Grants for Clinical Research for Evidenced Based Medicine, Health and Labour Sciences Research Grant for Clinical Cancer Research, and Grants-in Aid for Clinical Cancer Research (17S-1, 17S-5, 20S-1 and 20S-6) from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

The primary endpoint of the study is overall survival. Secondary endpoints are progression-free survival, response rates, adverse events, severe adverse events and the proportion of non-hospitalization periods compared with planned treatment periods. The last endpoint is intended to evaluate the reduced inconveniency of hospitalization with TC therapy as a surrogate for quality of life (QOL).

Eligibility Criteria

Inclusion Criteria

The inclusion criteria are as follows: (i) histologically proven uterine cervical cancer; (ii) squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma of the uterine cervix; (iii) one of the following: (a) newly diagnosed Stage IVB cervical cancer, (b) first relapse or persistent cervical cancer after curative or palliative first-line treatments, and (c) second relapse or persistent cervical cancer after curative or palliative second-line treatments including radiation therapy, chemotherapy, hormonal therapy or vaccination therapy; (iv) one of the following: (a) at least one metastatic lesion outside the pelvic cavity except in the paraaortic lymph node (LN) and/or inguinal LN, (b) no metastatic lesions outside the pelvic cavity except in the paraaortic LN and/or inguinal LN, and at least one of these lesions has been irradiated, and (c) all lesions are localized inside the pelvic cavity, and at least one of them has been irradiated; (v) recovery from effects of any prior therapy (at least 2 weeks from the last surgery or the last administration of chemotherapy alone, 3 weeks from radiotherapy alone and 4 weeks from the last administration of concurrent chemoradiotherapy); (vi) no previous treatment with >51 Gy of palliative radiation therapy; (vii) no prior surgical resection of pulmonary metastases or radical resection of recurrent lesions inside the pelvic cavity including pelvic exenteration; (viii) no bilateral hydronephrosis; (ix) no prior chemotherapy, or only one platinum-containing regimen; (x) no prior chemotherapy including taxanes; (xi) age ≥ 20 and ≤ 75 years; (xii) an Eastern Cooperative Oncology Group performance status (PS) of 0–2; (xiii) sufficient marrow, liver, kidney function and normal ECG; and (xiv) written informed consent.

Exclusion Criteria

The exclusion criteria are as follows: (i) neurological disturbance with functional disorder; (ii) symptomatic central nervous system metastasis; (iii) hypersensitivity to alcohol; (iv) active bacterial infection; (v) hepatitis B surface antigen-positive; (vi) poorly controlled hypertension; (vii) history of myocardiac infarction within 6 months; (viii) unstable angina; (ix) poorly controlled diabetes; (x) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*; (xi) pregnant or lactating; (xii) mental disease or mental symptoms that would affect the participant's decision to participate; and (xiii) continuous systemic steroid therapy.

Treatment Methods

Chemotherapy is administered as follows. The TP regimen (standard arm) is paclitaxel 135 mg/m^2 intravenously (IV) for 24 h on day 1, followed by cisplatin 50 mg/m^2 IV for 2 h on day 2, which is repeated every 21 days. The TC regimen

(experimental arm) is paclitaxel 175 mg/m^2 IV for 3 h on day 1, followed by carboplatin at an area under the curve of 5 IV for 1 h on day 1, which is repeated every 21 days. The premedication for paclitaxel with steroids, H1 blocker and H2 blocker is mandatory in both arms. Both regimens are administered for a maximum of six cycles for both responders and non-responders, or until disease progression or unacceptable toxicity prohibited additional therapy.

The Common Terminology Criteria for Adverse Events (CTCAE v3.0) is used for dose modifications. All patients are required to have absolute neutrophil counts $>1500/mm^3$, platelet counts $>75\,000/mm^3$ and acceptable levels of some non-hematologic toxicities <3 days before the treatment course or treatment is delayed until blood counts and non-hematologic toxicities return to acceptable levels. At the time of re-treatment, chemotherapy doses are adjusted based on nadir blood counts and interval toxicity. If necessary, patients are permitted to receive filgrastim.

A response was defined according to the RECIST criteria and generally evaluated after three courses and/or the last course of therapy.

Follow-up

All patients are followed up for 1 year after the study is closed for entry. Neurological adverse events are checked every 4 weeks, and the efficacy assessments are evaluated every 2 or 3 months.

Study Design and Statistical Methods

This study was designed as a randomized Phase III trial to demonstrate the non-inferiority of TC compared with standard TP using overall survival as the primary endpoint. Patients are randomized to each treatment arm by a minimization method with institution, PS (0, 1 or 2), histology (squamous cell carcinoma or adenocarcinoma) and tumor sites (all of them had prior radiotherapy or chemoradiotherapy or no therapy) as balancing factors at the JCOG Data Center (5,6). If TC is not inferior to TP in terms of overall survival and is comprehensively superior in terms of other secondary endpoints of safety or QOL, TC will be the preferred treatment. The corresponding null hypothesis is that the hazard ratio of TC to TP is >1.29, the non-inferiority margin. It corresponds that the mean survival time (MST) of TC is inferior to TP (9 months) by >2 months under the proportional hazard assumption. Assuming exponential distributions and that the MST of TC is 10 months, 234 patients are needed to have $>80\%$ power to confirm the non-inferiority with one-sided α 5% after a 1-year follow-up period with 2.5 years of accrual. Even if MST of TC is 9.5 months, at least 70% of power is attained by 242 patients. On the basis of these considerations, the planned sample size is 250.

The primary endpoint is to be analyzed based on the Cox proportional hazard model with PS and histology as stratified factors. If the upper limit of the 90% confidence interval of the hazard ratio is <1.29, the non-inferiority of TC to TP in terms of overall survival is confirmed. This study started in February 2006 with a planned accrual period of 2.5 years. The accrual of it, however, had been slow and the accrual period was revised to 3.5 years.

Interim Analysis and Monitoring

Interim analysis is scheduled once when half of the planned sample size has been accumulated and just after the nearest periodical monitoring data are available. Multiplicity is adjusted by the Lan and DeMets method with O'Brien and Fleming type boundaries. The Data and Safety Monitoring Committee (DSMC) of the JCOG will independently review the interim analysis report and determine whether the study should be stopped early. In-house interim monitoring will be performed by the JCOG Data Center to ensure data submission and study progress. The monitoring reports will be submitted to and reviewed by the GCSG every 6 months.

PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

Hokkaido University Hospital, Sapporo Medical University, Tohoku University Hospital, Institute of Clinical Medicine, Tsukuba University Hospital, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center (Saitama Medical School), Jikei Kashiwa Hospital, National Cancer Center Hospital, Jikei University Hospital, Cancer Institute Hospital, The University of Tokyo Hospital, Juntendo University School of Medicine, Kitasato University School of Medicine, Niigata Cancer Center Hospital, Sinshu University, Aichi Cancer Center Hospital, Osaka City University Medical School, Kinki University School of Medicine, Kyoto University Hospital, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka City General Hospital, Sakai Hospital, Kinki University School of Medicine, Hyogo Cancer Center Hospital, Faculty of Medicine, Tottori University, National Hospital Organization Kure Medical Center Chugoku Cancer Center, National Hospital Organization Shikoku Cancer Center, National Kyushu Cancer Center, Kurume University School of Medicine, Kyushu University Hospital, Faculty of Medicine, Saga University and Kagoshima City Hospital.

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Conflict of interest statement

None declared.

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Feasibility study of neoadjuvant chemotherapy followed by interval debulking surgery for stage III/IV ovarian, tubal, and peritoneal cancers: Japan Clinical Oncology Group Study JCOG0206☆,☆☆

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ABSTRACT

Background. To assess the safety and efficacy of neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) for müllerian carcinomas, such as ovarian, tubal, and peritoneal cancers, and to determine whether we can omit diagnostic laparoscopy before treatment initiation, a feasibility study was performed.

Methods. Eligible patients had presumed stage III/IV müllerian carcinomas clinically diagnosed by imaging studies, cytology, and tumor markers. All patients underwent diagnostic laparoscopy to confirm the clinical diagnosis. Four cycles of paclitaxel and carboplatin were administered as NAC, followed by interval debulking surgery and an additional 4 cycles of chemotherapy. The primary end point was the proportion of patients achieving clinical complete remission (cCR) among all stage III/IV müllerian carcinomas confirmed by diagnostic laparoscopy. The major secondary end point was the positive predictive value (PPV) of clinical diagnosis.

Results. Fifty-six patients were enrolled into the study. The PPV of overall clinical diagnosis for the tumor origin, histology, and stage was 95% (53/56). Fifty-three patients received the protocol treatment starting with NAC. IDS was performed in 89% (47/53) of patients. Complete resection without residual tumors was achieved in 55% (29/53) and residual tumors became <1 cm in 17% (9/53) of patients. Twenty-two patients (42%) achieved cCR after completion of the treatment. The median overall and progression-free survival was 45 and 14 months, respectively.

Conclusion. NAC without diagnostic laparoscopy for advanced müllerian carcinomas holds sufficient promise to be compared with direct surgery in a phase III trial.

Introduction

The standard treatment for advanced müllerian cancer (MC), such as ovarian, tubal, and peritoneal cancer, is primary debulking surgery (PDS) and postoperative chemotherapy. Previous studies have demonstrated that optimal debulking at the time of primary surgery improves patient survival [1–3]. Though optimal resection rates of experienced centers on gynecologic oncology reach up to 90%, optimal debulking can be achieved in only 30–60% of stage III/IV ovarian cancers in average institutions [1,2].

Retrospective analyses [4–7] have revealed that survival of the patients who received neoadjuvant chemotherapy (NAC) is comparable to that of patients who underwent direct PDS, even though the former group was older with more advanced disease and had a poorer performance status (PS). Thus, NAC appears to be useful at least for patients with far advanced ovarian cancer. However, NAC is allowed as an alternative to the standard treatment only in MC

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☆☆ This study is registered with Clinicaltrials.gov (identification number: NCT00112086) and with UMIN-CTR [www.umin.ac.jp/ctr/] (identification number: C000000005).

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patients with apparently unresectable bulky tumors or poor PS (NCCN guidelines).

European Organization for Research and Treatment of Cancer (EORTC) started a phase III study comparing NAC with the standard treatment for advanced MC [8] and thereafter, Medical Research Council Clinical Trials Unit (CTU-MRC) started similar phase III study in 2004 [identification number in Clinicaltrials.gov: NCT00075712]. In 2002, we also planned to conduct a phase III trial to compare NAC and direct PDS. At that time, we had little experience with NAC for treatment of advanced MC, including the possibly resectable cases. Thus, we planned to conduct a feasibility study of NAC before a phase III trial. The main purpose of the study was to assess the safety and efficacy of NAC with paclitaxel and carboplatin for advanced MC. The other purpose was to determine whether omission of the diagnostic laparoscopy (DLS) before NAC for advanced MC is possible by the use of imaging studies, cytological findings, and tumor markers. According to the current treatment guidelines, DLS or laparotomy to confirm the diagnosis and stage before NAC is mandatory. However, these procedures lead to a delay in the initiation of treatment and nullify the advantage of less invasiveness of NAC. Therefore, if ethically and medically acceptable, it seems desirable to omit the diagnostic procedure in the phase III trial.

The study protocol was designed by the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG) and was approved by the Clinical Trial Review Committee of JCOG on 6 December 2002 and activated on 14 January 2003 [9].

Patients and methods

Patient selection

The study subjects were patients with presumed stage III/IV MC clinically diagnosed by imaging studies (CT [computed tomography] or MRI [magnetic resonance imaging]) and cytological examination of ascites, pleural effusions, or fluids obtained by tumor centesis. Stage IV disease was diagnosed according to the routine FIGO staging. Diagnosis of stage III disease based on retroperitoneal lymph node metastasis was allowed only when swollen nodes were suspicious for metastasis by imaging studies and >2 cm in diameter. Malignancies of other origins, such as the breast and the digestive tract, when suspected from symptoms, physical examinations, or imaging studies, were ruled out by ultrasonography, endoscopy, or opaque enema. To efficiently rule out malignancies originating from the digestive tract, the criteria for the tumor markers were set as CA125 >200 U/ml and CEA <20 ng/ml. The further inclusion criteria were as follows: clinically deemed to be a candidate for debulking surgery without evidence of brain, bone, bone marrow, or multiple lung or liver metastases; presence of at least one measurable lesion; previously untreated for these malignancies and no history of treatment with chemotherapy or radiotherapy even for other diseases; aged between 20 and 75 years; Eastern Cooperative Oncology Group (ECOG) PS of 0 to 3; adequate organ functions; and written informed consent.

The exclusion criteria include intestinal occlusion necessary for surgical treatment; hypersensitivity to alcohol; and severe medical complications. More details of eligibility criteria were described previously [9].

Treatment plan

After enrollment, DLS was performed. Inspection of peritoneal cavity and biopsy from the main tumor or metastatic tumors was performed to confirm the clinical diagnosis of the origin, histology, and stage.

Four cycles of a combination of intravenous paclitaxel [over 3 h; day 1] and carboplatin [day 1], i.e., TC, were administered every 3 weeks as NAC. Before paclitaxel was administered, standard short premedication was used to avoid anaphylactic reactions. The dose of carboplatin was calculated from the formula of Calvert [10]. The creatinine clearance by the Cockcroft–Gault [11] equation was used as the glomerular filtration rate (GFR) in the formula. The creatinine clearance, body weight, and body surface area on entry into the study were used during all 4 cycles of NAC.

Interval debulking surgery (IDS) was performed after the fourth cycle of NAC, unless there was evidence of disease progression. The standard procedures in IDS comprised total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and maximal debulking of the metastatic tumors. Systematic pelvic and/or paraaortic lymphadenectomies were allowed, but not included in the standard procedure.

After IDS, an additional 4 cycles of chemotherapy was administered as postoperative chemotherapy (8 cycles in all). The creatinine clearance, body weight, and body surface area between IDS and the first cycle of postoperative chemotherapy were used during all 4 cycles of postoperative chemotherapy.

Modification of the treatment

Four dose levels were set for both paclitaxel and carboplatin. The initial dose of paclitaxel was 175 mg/m^2 (level 0), and the dose was reduced to 130 mg/m^2 (level −3) in decrements of 15 mg/m^2. The dose of carboplatin was reduced from the starting targeted area under the curve (AUC) of 6 (level 0) to 5, 4.5, and 4 (level −3) in a step-by-step manner. Even when the toxicities disappeared, the dose level was not restored to the previous dose level. The level during NAC was carried forward to postoperative chemotherapy.

Hematological toxicities that required a dose reduction of 1 level of both agents were grade 4 neutropenia observed in an interval of >3 days in the same cycle, neutropenic fever observed in an interval of >1 day in the same cycle, and grade 3 thrombocytopenia. Neurotoxicity that required a dose reduction of 1 level of paclitaxel alone was grade 2 sensory-neuropathy.

When the toxicities that required dose reduction were observed at the lowest level, or grade 3 sensory-neuropathy was observed at any dose level, the treatment protocol was discontinued. The other discontinuation criteria were progression of the disease, delay of chemotherapy for >2 weeks, delay of surgery from the planned time period, grade 3 allergic-reaction/hypersensitivity, grade 4 non-hematological toxicities, and misdiagnosis confirmed by DLS.

End points

The primary end point was the proportion of clinical complete remission (%cCR) among all patients with stage III/IV MC, whose diagnosis was confirmed by DLS. Clinical complete remission was defined as the disappearance of all lesions on CT or MRI, no pleural effusion on chest radiography, and a serum CA125 level of <20 U/ml upon completion of the treatment.

The secondary end points were positive predictive value (PPV) of the clinical diagnosis with regard to the origin and histology, FIGO stage, and overall clinical diagnosis among all the participants. The PPV of overall clinical diagnosis was the end point to decide whether we could omit DLS in the subsequent phase III study. Because laparoscopy was performed only in patients diagnosed as stage III/IV MC by clinical findings, it was not possible to use sensitivity or specificity to evaluate the accuracy of clinical diagnoses, therefore we adopted PPV. With regard to the histology, the histological diagnosis compatible with any of the epithelial ovarian carcinomas was considered as correct diagnosis. Concerning the diagnosis of stage, surgical stage III was considered as correct even if substage was different from prelaparoscopic stage III substage. Regarding prelaparoscopic stage IV disease, the diagnosis of the stage was correct irrespective of the peritoneal findings on DLS.