recently published [4]. Results from other Phase III studies conducted in the UK, India and Japan are expected in the next few years. In this article, we review the outcomes of NACT, focusing on a comparison with that of PDS setting treatment, and discuss some of the questions concerning NACT.

Outcome of NACT

Comparable outcomes & reduced morbidity of NACT compared with PDS-CT in retrospective & prospective, nonrandomized comparative studies

To date, numerous retrospective studies reporting treatment results and complications of NACT have been published. Among these, studies comparing treatment outcomes (Table 1) [5–16] and complications related to debulking surgery (Table 2) [5,7,8,10,12,14–17] between PDS-CT and NACT are summarized. In most of the studies, NACT was administered to patients who had older age, more advanced disease or a lower PS, whereas characteristics of subjects for NACT and PDS-CT were not statistically different in studies by Jacob *et al.* [5], Vrščaj *et al.* [9] and Morice *et al.* [10]. In these highly biased settings unfavorable to NACT, all of the studies showed a similar or higher proportion of optimal debulking surgery in NACT, and all but one study by Steed *et al.* yielded noninferior outcomes of NACT compared with those of PDS-CT (Table 1) [14]. After controlling for age, the International Federation of Gynecology and Obstetrics stage, histologic grade and pleural effusions, even the study by Steed *et al.*, demonstrated no statistical difference in overall survival (OS; p = 0.95) between NACT and PDS-CT. As for the invasiveness of debulking surgery,

Table 1. Comparison of outcomes between primary debulking surgery followed by chemotherapy and neoadjuvant chemotherapy-setting treatment in retrospective studies.

Study (year)	Treatment	Patients (n)	Survival		Optimal surgery		Ref.
			MST	Survival curves	Residual tumor (cm)	Proportion (%)	Significance	
Jacob *et al.* (1991)	PDS-CT	18	18 months		<2	39 (7/18)		[5]
	NACT	22	16 months	NS	<2	77 (17/22)	p = 0.02	
Onnis *et al.* (1996)	PDS-CT	284	21%†		<2	29 (83/284)		[6]
	NACT	88	19%†	NS	<2 cm	42 (37/88)	p = 0.027§	
Schwartz *et al.* (1999)	PDS-CT	206	2.18 years		NA	NA		[7]
	NACT	59	1.07 years	NS	NA	NA		
Kayikçioğlu *et al.* (2001)	PDS-CT	158	38 months		0	14 (22/158)		[8]
	NACT	45	34 months	NS	0	49 (22/45)	p < 0.001	
Vrščaj *et al.* (2002)	PDS-CT	55	26 months		<1	22 (12/55)		[9]
	NACT	20	25 months	NS	<1	60 (12/20)	p = 0.001	
Morice *et al.* (2003)	PDS-CT	34	22 months		<2	94 (32/34)		[10]
	NACT	34	26 months	NS	<2	94 (32/34)	NS	
Loizzi *et al.* (2005)	PDS-CT	30	40 months		<1	60 (18/30)		[11]
	NACT	30	32 months	NS	<1	63 (19/30)‡	NS§	
Everett *et al.* (2006)	PDS-CT	102	42 months		<1	54 (55/102)		[12]
	NACT	98	33 months	NS	<1	86 (84/98)	p < 0.001	
Inciura *et al.* (2006)	PDS-CT	361	25 months		<2	67 (242/361)		[13]
	NACT	213	24 months	NS	<2	63 (134/213)	NS	
Steed *et al.* (2006)	PDS-CT	66	3.7 years		<2	50 (33/66)		[14]
	NACT	50	2.4 years	p = 0.03	<2	52 (26/50)‡	NS§	
Hou *et al.* (2007)	PDS-CT	109	47 months		<1	71 (77/109)		[15]
	NACT	63	46 months	NS	<1	95 (60/63)	<0.001	
Colombo *et al.* (2009)	PDS-CT	142	38 months		<1	63 (89/142)		[16]
	NACT	61	26 months	NA	<1	84 (51/61)	p = 0.003§	

†Shows 5-year survival rates.
‡Recalculated as to include all patients into denominators.
§Calculated using Fisher's exact test because the values are not available.
MST: Median survival time; NA: Not available; NACT: Neoadjuvant chemotherapy-setting treatment; NS: Not significant; PDS-CT: Primary debulking surgery followed by chemotherapy.

Table 2. Comparison of surgical invasiveness between primary debulking surgery and interval debulking surgery in retrospective studies.

Study (year)	Treatment	Patients (n)	Blood loss	Bowel resection	Diaphragm resection	Splenectomy	Stay in ICU	Duration of hospitalization	Ref.
Jacob *et al.* (1991)	PDS-CT	18	44% (>2000 ml)						[5]
	NACT	22	31% (>2000 ml)						
			NA						
Schwartz *et al.* (1999)	PDS-CT	206	1000 ml				1.26 days	11 days	[7]
	NACT	59	600 ml				1.03 days	7 days	
			p = 0.001				p = 0.01	p < 0.001	
Kayikçioğlu *et al.* (2001)	PDS-CT	158		16% (colon)	11%				[8]
	NACT	45		2% (colon)	0%				
				p = 0.01	p = 0.02				
Morice *et al.* (2003)	PDS-CT	28	39%	61%	7%	36% (severe)			[17]
	NACT	57	21%	19%	5%	7% (severe)			
			NS	p = 0.01	NS	p = 0.01			
Morice *et al.* (2003)	PDS-CT	34	56%	73%		53%	36%	20 days	[10]
	NACT	34	18%	18%		12%	12%	12 days	
			p < 0.001	p < 0.001		p < 0.001	p = 0.02	p < 0.001	
Everett *et al.* (2006)	PDS-CT	102	2.47 U	11%		15%	1.8 days	6 days	[12]
	NACT	98	3.02 U	16%		17%	1.5 days	6 days	
			NS	NS		NS	NS	NS	
Steed *et al.* (2006)	PDS-CT	66		5% (colon)					[14]
	NACT	50		2%† (colon)					
				NS					
Hou *et al.* (2007)	PDS-CT	109	1033 ml	22% (colon)	3%	34%	1.6 days	8.5 days	[15]
	NACT	63	546 ml	5%† (colon)	0%	28%†	2 days	5.7 days	
			p < 0.0001	p = 0.004‡	NA	NS	NS	p < 0.0001	
Colombo *et al.* (2009)	PDS-CT	142		51%	4%	12% (major)		14 days	[16]
	NACT	61		51%	8%	13% (major)		14 days	
				NA	NS‡	NS		NS	

†Patients who did not underwent interval debulking surgery are not included in denominators.
‡Calculated using Fisher's exact test.
NA: Not available; NACT: Neoadjuvant chemotherapy-setting treatment; NS: Not significant; PDS-CT: Primary debulking surgery followed by chemotherapy.

several studies revealed significantly less invasiveness in the NACT group. For example, compared with the PDS group, the NACT group had a smaller amount of blood loss, lower rate or amount of blood transfusion, lower rate of bowel resection, lower rate of splenectomy, lower rate of surgical morbidities, shorter and less frequent stay in an intensive care unit (ICU) and shorter duration of hospitalization (Table 2). In addition to the benefits for the NACT group compared with the PDS-CT group described in Table 2, a significantly lower frequency of tumor invasion to the appendix (22 vs 80%; $p < 0.001$) [8], a lower rate of permanent colostomy (6 vs 24%; $p = 0.04$) [10], a lower rate of complications requiring surgery (3 vs 21%; $p = 0.03$) [10], and a shorter duration of surgery (211 vs 276 min; $p < 0.0001$) [15] were also reported.

Kuhn *et al.* [18], Hegazy *et al.* [19] and Lee *et al.* [20] conducted similar comparisons by nonrandomized, prospective studies (Table 3). Kuhn *et al.* offered a NACT protocol to patients with stage IIIC ovarian cancer with an estimated >500 ml of ascites [18]. Patients who agreed with the proposal received NACT, and the other patients who refused the proposal received conventional PDS-CT treatment. The characteristics of these two groups were not statistically different. Compared with the PDS-CT group, there was a higher proportion of optimal surgeries in the NACT group and an improved median survival time (MST) in the NACT group.

Hegazy *et al.* chose NACT or PDS-CT for the patients with stage III/IV ovarian cancer according to tumor resectability estimated by diagnostic laparotomy or laparoscopy. Patients who received NACT because of tumor unresectability were older than the patients who received PDS-CT (average age: 58.7 vs 53.6 years, respectively; $p = 0.04$) [19]. They reported no difference in proportion of optimal surgery and OS.

Lee *et al.* selected patients who received NACT for stage IIIC/IV ovarian cancer according to diagnoses based on imaging studies, such as computed tomography (CT) or MRI [20]. Patients who refused NACT received PDS-CT. The characteristics of these two groups were not statistically different. Compared with the PDS-CT group, there was a higher proportion of optimal surgery in the NACT group, but the improvement did not impact survival.

As for surgical invasiveness of NACT compared with PDS-CT, two studies [19,20] showed statistically significant reductions of blood loss, and one study showed a reduction in the duration of ICU stay and hospitalization [19].

Giannopoulos *et al.* compared the parameters of surgical invasiveness between PDS-CT (n = 29) and NACT (n = 35) in the treatment of stage IIIC/IV ovarian cancer [21]. Patients treated with NACT were nonrandomly selected according to the unresectability of tumors evaluated by laparoscopy or CT imaging. They demonstrated that median, intraoperative blood loss (500 vs 1000 ml; $p = 0.043$), median hospital stay (7 vs 8 days; $p = 0.005$), and possibility of admission to the ICU (5.7 vs 48.3%; $p < 0.001$) were significantly less in the NACT group than in the PDS-CT group.

From these retrospective or nonrandomized, prospective, comparative studies, NACT did not seem to compromise the survival of patients with advanced-stage ovarian, tubal or peritoneal cancer and seemed to greatly reduce surgical invasiveness.

Increased possibility of optimal surgery by NACT but rather poor survival in meta-analyses

Bristow *et al.* selected 22 cohorts from 21 studies and performed a meta-analysis in order to determine the OS and relative effect of multiple, prognostic variables in cohorts of patients with advanced-stage ovarian cancer treated with NACT (Table 4) [22]. The main selection criteria for the study were:

- Subjects were predominantly (>90%) patients with stage III/IV epithelial ovarian cancer;
- Subjects underwent NAC that included cisplatin (CDDP) or carboplatin (CBDCA);
- Subjects underwent NAC prior to cytoreductive surgery.

The target period for the Medline search was from 1 January 1989 to 30 September 2005. Using linear regression models, the effects of six variables (i.e., the proportion of maximal interval cytoreduction, stage IV disease, taxane use, median number of NAC cycles, median age and year of publication) on MST were assessed. The weighted mean MST was 24.5 months, and the weighted mean proportion of maximum cytoreduction was 65.0%. All variables other than median age were significantly correlated to MST. Each 10% increase in maximum cytoreduction was associated with a 1.9-month increase in MST, and each incremental increase in NAC cycles was associated with a 4.1-month decrease in MST. The authors reported that the survival outcome of NAC was equivalent to that of suboptimal PDS (>1 cm) followed by six cycles of CDDP and cyclophosphamide in the Gynecologic Oncology Group (GOG) 111 trial (24.5 vs 24 months). They concluded that NACT is associated with inferior OS compared with PDS-CT. However, this conclusion was not surprising because NACT was initially predominantly administered to older patients, with more advanced-stage disease, or patients with low PS, as mentioned earlier.

Recently, Kang *et al.* published the results of a similar meta-analysis (Table 4) [23]. The main selection criteria for this study were identical with the preceding study. The target period for the Medline search was extended until 30 June 2008. Although the number of selected studies were the same, seven studies were excluded and seven newer studies were included. To produce more reliable results, they chose a random-effects model instead of a simple linear regression model. The weighted mean MST was 27.5 months, and the weighted mean proportion of maximum cytoreduction was 70.0%. Again, the proportion of maximal interval cytoreduction, taxane use and year of publication were significantly associated with MST. However, the proportion of stage IV disease and median number of NAC cycles did not have a statistically significant association with MST. Furthermore, they examined ten comparative studies between NACT and PDS-CT, and analyzed the proportion of optimal cytoreduction. They found that the risk of suboptimal cytoreduction in the NACT group was reduced to 0.5 (95% CI: 0.29–0.86; $p = 0.012$) compared with the PDS-CT group, and concluded that NACT helped gynecologic oncologists to achieve an increased rate of optimal cytoreduction.

Table 3. Comparison between primary debulking surgery followed by chemotherapy and neoadjuvant chemotherapy-setting treatment in nonrandomized prospective studies.

Variables/comparison	Kuhn et al.			Hegg et al.			Sehouli et al.		
	PDS-CT (n = 32)	NACT (n = 31)	p-value	PDS-CT (n = 27)	NACT (n = 27)	p-value	PDS-CT (n = 22)	NACT (n = 18)	p-value
Characteristics									
Age (years)	66 (median)	61 (median)	NS	53.6	58.7	p = 0.04	46.8	45.0	NS
Performance status 2 (%)							32	28	NS
Stage IV (%)				56	59	NS	9	11	NS
Perioperative results									
Performance of IDS		97% (30/31)			67% (18/27)			100% (18/18)	
Definition of optimal surgery	<2 cm	<2 cm		<1 cm	<1 cm		<2 cm	<2 cm	
Proportion of optimal surgery	63% (20/32)	84% (26/31)	p = 0.04	62% (20/32)	48% (13/27)	NS	46% (10/22)	78% (14/18)	p = 0.04
Blood loss				735 ml	420 ml	p = 0.02	1061 ml	620 ml	p = 0.04
Blood transfusion (median)	2 U	2 U	NS						
Duration of surgery	270 min	260 min	NS	190 min	150 min	NS			
Duration of ICU stay				4.4 days	1.7 days	p = 0.03			
Duration of hospitalization				15.9 days	10.5 days	p < 0.05	10.4 days	9.7 days	NS
Organ resection (n)									
Intestinal resection	11	9	NS				3	1	NA
Other organ resection				11 in total	4 in total	NS	2	0	NA
Complications (n)									
Ileus	3	0	NS						
Wound infection				2	2	NS			
Wound dehiscence	1	3	NS						
Fever >3 days	7	2	NS	7	1	NS			
Cystitis	2	1	NS						
Atelectasis	1	1	NS	1	1	NS			
Pleural effusion				2	0	NS			
Thromboembolism	1	1	NS	3	1	NS			
Prognosis									
MST	23 months	42 months	p = 0.007	28 months	25 months	NS	55 months	53 months	NS
PFS				19 months	21 months	NS	17 months	15 months	NS

IDS: Interval debulking surgery; MST: Median survival time; NA: Not available; NACT: Neoadjuvant chemotherapy-setting treatment; NS: Not significant; PDS-CT: Primary debulking surgery followed by chemotherapy; PFI: Progression-free interval; PFS: Progression-free survival.

Final comparisons by prospective, randomized Phase III trials

Although NACT seems to be a promising approach for the treatment of patients with advanced-stage ovarian cancer, to become a standard treatment, it is necessary to demonstrate the superiority of NACT in treatment outcome or to show the noninferiority of NACT in treatment outcome and lower toxicity compared with PDS-CT. The most reliable and quickest way to demonstrate superiority or noninferiority of NACT is to conduct a randomized Phase III study comparing NACT and PDS-CT. Until now, at least four Phase III studies have begun in Europe [4,24], India (ClinicalTrials.gov identifier: NCT00715286 [101]) and Japan (TABLE 5) [25]. Subjects were patients with stage III/IV or IIIC/IV disease. In all studies, patients who were not suitable for PDS because of medical contraindication or poor PS were excluded. Target diseases included not only ovarian cancer but also tubal and peritoneal cancers in three European or Japanese studies.

The results of the earliest study by Vergote *et al.* in the EORTC trial (EORTC55971) have recently been published [4]. They compared NACT, which consisted of three cycles of NAC followed by IDS, and three cycles of postsurgical chemotherapy with PDS-CT, consisting of PDS followed by six cycles of postsurgical chemotherapy. The chemotherapy regimen was a combination of platinum and taxane chosen by each institution. Patients with biopsy- or cytology-proven stage IIIC/IV ovarian, tubal or peritoneal cancer were enrolled in the study. The study was open from September 1999 to December 2006 and 718 patients were enrolled. The outcome of 670 patients randomized into two treatment arms was analyzed. The largest residual tumor was ≤1 cm in diameter in 41.6% of patients after PDS and in 80.6% of patients after IDS. Although statistical analyses were not performed, postoperative infections, venous complications, fistula, hemorrhage and postoperative mortality tended to be lower after IDS in the NACT group than after PDS. The MST was 29 months in the PDS-CT group and 30 months in the NACT group, and the median progression-free survival (PFS) in both groups was 12 months in the intent-to-treat analysis. The hazard ratio for death in the NACT group compared with that in the PDS-CT group was 0.98 (90% CI: 0.84–1.13; p = 0.01 for noninferiority). They concluded that NACT was not inferior to PDS-CT as a treatment option for patients with bulky stage IIIC/IV ovarian carcinoma.

In March 2004, Kehoe *et al.* at the Medical Research Council Clinical Trials Unit (MRC-CTU) had started a Phase III part of a Phase II/III study named Chemotherapy or Upfront Surgery (CHORUS) [24]. The planned accrual number was 150 individuals in the Phase II part and 400 in Phase III part. The Phase III part of the study closed in August 2010. One of the distinct characteristics of the study was that patients were enrolled into the study based only on imaging diagnosis without cytological or histological confirmation. Other characteristics included that the chemotherapy regimen was a single-agent CBDCA or a combination with other agents chosen for each patient, and that the study was designed to demonstrate the noninferiority of NACT in OS by combining the data with that from the EORTC 55971 trial. The follow-up data are still accumulating, thus the results of the study have not yet been published.

The Japan Clinical Oncology Group (JCOG) conducted a similar Phase III study (JCOG0602) [25] after successfully completing a feasibility study (JCOG0206) [26,27]. Patients were enrolled into the study with a clinical diagnosis of stage III/IV ovarian, tubal or peritoneal cancer based on imaging studies, cytological diagnoses, serum CA125 (>200 U/ml) and carcinoembryonic antigen (CEA) titer (<20 ng/ml). Histological diagnosis, instead of cytology, was allowed in patients with available lesions without laparoscopy or laparotomy. Diagnostic laparoscopy or laparotomy after enrollment was not performed because their preceding feasibility study showed that target disease (i.e., stage III/IV ovarian, tubal and peritoneal cancer) can be diagnosed reliably using the same criteria adopted in this study. This means eliminating an extra surgical procedure for the purpose of the clinical trial in both treatment arms, and it has the advantage of allowing NACT to start earlier. Other special characteristics of the study were that the regimen of chemotherapy was restricted to a combination of paclitaxel (PTX) and CBDCA, the number of cycles of NAC was four, and the number of cycles of chemotherapy was eight in total, considering the advanced stage of the subjects.

Kumar *et al.* from the All India Institute of Medical Sciences are conducting a Phase III study. They set the target disease as stage IIIC/IV ovarian cancer [28,29]. Stage IV disease was restricted to disease upstaged owing to pleural effusion. Cytological or histological diagnosis was necessary before enrollment. The study started in November 2001 and is open according to information last updated on 14 July 2008 (ClinicalTrials.gov identifier: NCT00715286 [101]).

From the favorable results of the EORTC study, NACT may be one of treatment options available for patients with bulky stage IIIC or IV ovarian, tubal and peritoneal cancer. Furthermore, NACT would be expected to become a standard treatment for unselected patients with advanced ovarian cancer when favorable results are confirmed and several problems are resolved by the following studies.

Problems & questions about NACT

As NACT becomes more widely used, several problems that should be solved or questions that should be answered will arise. We will discuss some of these important issues next.

How should target diseases be diagnosed before NACT?

In the PDS-CT treatment setting, the aims of surgery are to confirm the diagnosis of ovarian, tubal or peritoneal cancer; determine an accurate stage of the disease; and reduce bulky tumors.

We understand that it is necessary in principle to perform diagnostic laparoscopy or laparotomy in order to confirm diagnosis and stage of the disease before chemotherapy also in the setting of NACT. However, the procedure may spoil the merits of NACT, such as less-invasiveness and immediate initiation of treatment. How to quickly and accurately confirm the diagnosis of the disease before NACT is a major problem.

The MRC-CTU study allowed patients to enroll on the basis of diagnoses using imaging studies without cytological or histological confirmation [24]. To exclude gastrointestinal cancer,

Table 4. Results of meta-analyses for neoadjuvant chemotherapy-setting treatment.

	[illegible]	[illegible]
Major selection criteria:	– Stage III/IV>90% – NAC regimen included CDDP or CBDCA – NAC was administered before cytoreductive surgery	
Target period for Medline search	1 January 1989–30 September 2005	1 January 1989–30 June 2008
Studies (n)	21	21
[illegible]		
MST	24.5 months	27.5 months
Taxane use (%)	47.7	48.2
Optimal cytoreduction (%)	65.0	70.0
Stage IV (%)	27.4	28.9
Age (years)	61.1	60.4
[illegible]		
Year of publication	p = 0.004 (1.1 months/year)	p = 0.002
Rate of taxane use	p < 0.0005 (1.6 months/10%)	p = 0.007
Rate of optimal cytoreduction	p = 0.012 (1.9 months/10%)	p = 0.012
Rate of stage IV patients	p = 0.002 (-2.3 months/10%)	p = 0.101 (NS)
NAC cycles (n)	p = 0.046 (-4.1 months/cycle)	p = 0.701 (NS)
Age	p = 0.448 (NS)	NA
Statistical method	Simple linear regression model	Random-effects model

CBDCA: Carboplatin; CDDP: Cisplatin; MST: Median survival time; NA: Not assessed; NAC: Neoadjuvant chemotherapy; NS: Not significant.

the tumor marker criterion (CA125/CEA ratio >25) could be used. After enrollment, patients assigned to NACT required laparoscopic biopsy, image-guided biopsy or fine-needle biopsy. Although the rate of benign disease or the rate of other malignancy may be revealed by the study, at present we cannot recommend starting NACT by using only diagnoses based on imaging tests and serum tumor marker results.

Schwartz *et al.* evaluated the role of cytology in the pretreatment diagnosis of advanced-stage ovarian cancer [30]. They performed NACT for patients with advanced-stage ovarian cancer diagnosed based on clinical findings. Pretreatment cytology slides of ascitic fluid were reviewed and categorized as consistent with ovarian cancer, not consistent with ovarian cancer, or insufficient. Pathological diagnosis at IDS and cytological diagnosis were compared in 47 patients. In total, 42 out of 43 patients with cytology consistent with ovarian cancer had ovarian cancer and one had no pathologic evidence of disease. Two out of three patients with cytology not consistent with ovarian cancer had ovarian cancer, and one had a mesonephric adenocarcinoma. The authors conclude that cytology has proven to be extremely helpful in supporting clinical impressions of apparently advanced-stage ovarian cancer.

Freedman *et al.* compared diagnostic strategies for predicting final pathology of ovarian cancer among 149 patients who underwent NACT [31]. The initial diagnosis was based on cytology in 108 patients, histology in 26 patients and only clinical factors (imaging studies and CA125) in 15 patients. Pathological diagnoses of disease in four patients who obtained complete pathological responses were determined to be consistent with ovarian cancer. The diagnostic accuracy of the cytology, histology and clinical factors alone was 98, 96 and 87%, respectively (p = 0.04). The authors conclude that diagnosis of epithelial ovarian cancer based on cytology and histology are superior to clinical factors alone.

The JCOG0206 study assessed the accuracy of clinical diagnosis based on imaging tests, cytology from ascites, pleural effusion or tumor, and tumor markers (CA125 >200 U/ml and CEA <20 ng/ml) [27]. All enrolled patients underwent diagnostic laparoscopy in order to determine accurate diagnoses. The disease was ovarian, tubal or peritoneal cancer in 100% (56 out of 56 patients), and stage III/IV in 95% (53 out of 56 patients). As for the stage of the disease, laparotomy performed immediately after the diagnostic laparoscopy revealed stage IIIb disease in one out of the aforementioned three patients. The results suggest that appropriate target diseases for NACT can be diagnosed with >90% accuracy by clinical diagnoses based on findings including cytology, according to the Bayesian statistical methods.

From these studies, it can be concluded that cytological examination of ascites, pleural effusion or tumor in addition to imaging diagnosis and tumor markers may be necessary before NACT for accurate diagnosis of advanced-stage ovarian, tubal or peritoneal cancer, unless we select diagnostic laparotomy or laparoscopy.

Table 5. Phase III randomized studies comparing neoadjuvant chemotherapy-setting treatment and primary debulking surgery followed by chemotherapy.

Study group	EORTC	CHORUS	JCOG	All India Institute of Medical Sciences
Study name or ID	EORTC55971	CHORUS	JCOG0602	ID I473
Principal Investigator	Vergote IB	Kehoe S	Yoshikawa H	Kumar L
Country or area	Europe	UK	Japan	India
Target disease origin	Ovary, tube and peritoneum	Ovary, tube and peritoneum	Ovary, tube and peritoneum	Ovary
Stage	Stage IIIC/IV	Stage III/IV	Stage III/IV	Stage IIIC + IV (pleural effusion)
Phase of the study	III	II/III	III	III
Cytology				
Necessity for biopsy/ cytology	Biopsy is preferentially necessary FNA cytology is allowed	Neither biopsy nor cytology is necessary	Cytology is necessary biopsy is allowed	Either biopsy or cytology is allowed
Tumor marker	CA125/CEA ratio >25†	CA125/CEA ratio >25‡	CA125 >200 U/ml; CEA <20 ng/ml	Normal CEA
Regimen	Platinum (CDDP or CBDCA) + taxane (PTX or DTX)	CBDCA or CBDCA based	PTX + CBDCA	PTX + CBDCA
Chemotherapy cycles (n)	NAC: 3/total: 6	NAC: 3/total: 6	NAC: 4/total: 8	NAC: 3/total: 6
Planned number of patients	704	150 (Phase II) + 400 (Phase III)	300	180
Start date	21 September 1998	March 2004 (Phase III part)	17 November 2006	November 2001
Accrual period	4 years	4 years	3 years	5 years
Status of the study	Closed on 6 December 2006	Closed on 31 August 2010	Open	Open
Design of the study	Noninferiority	Noninferiority (combined with EORTC patients)	Noninferiority	Noninferiority (probably)
Database registration ID	NCT00003636	NCT00075712	UMIN000000523	NCT00715286
Registered day	1 November 1999	9 January 2004	17 November 2006	14 July 2008

†Supplementary criterion to omit investigations for gastrointestinal or colon cancer in whom cytology was used for the confirmation of malignancy.
‡Supplementary criterion to omit investigations for gastrointestinal cancer.
CBDCA: Carboplatin; CDDP: Cisplatin; CEA: Carcinoembryonic antigen; CHORUS: Chemotherapy or Upfront Surgery; CTU-MRC: Medical Research Council Clinical Trials Unit; DTX: Docetaxel; EORTC: European Organization for Research and Treatment of Cancer; FNA: Fine-needle aspiration; JCOG: Japan Clinical Oncology Group; NAC: Neoadjuvant chemotherapy; PTX: Paclitaxel.

When should we perform IDS?

In earlier studies of NACT, the number of cycles of NAC was sometimes based on the response to NAC. Occasionally, the number of cycles of NAC reached more than six cycles in each patient base [7,32,33], while in more recent studies, the number of cycles of NAC usually settled at three or four cycles. However, the optimal number of cycles of NAC has not yet been determined. Some reports paid attention to the number of NAC cycles.

Lim and Green administered NAC to 30 patients with stage III/IV ovarian cancer [34]. The NAC regimen consisted of CBDCA, ifosfamide, and mesna for a median of three cycles. Objective responses were observed in 13 patients, including five patients who achieved a complete response after three cycles. This study showed that more than three cycles of NAC did not increase the number of complete responses, but were associated with greater toxicity. The use of three cycles was optimal in terms of the response rate, feasibility of beneficial surgery, and so on.

In a retrospective study by Loizzi *et al.*, 30 women were treated with NACT [11]. The mean number of NAC cycles was 4.1, and the NAC regimen consisted of CDDP and cyclophosphamide in 12 patients and PTX and CBDCA in 18 patients. In this study, the outcome of patients who underwent ≤three cycles of NAC were compared with those who received >three cycles. No statistically significant difference between the two groups was observed

Table 6. Summary of interval debulking surgery outcomes following neoadjuvant chemotherapy composed of platinum and taxane combination.

Kuhn *et al.* (2001)	31	3	CBDCA + PTX	97 (30/31)	84 (26/31)†	NR	32 (10/31)†	Prospective	[18]
Chan *et al.* (2003)	17	3	Platinum + PTX	76 (13/17)	59 (10/17)†	NR	29 (5/17)†	Retrospective	[52]
Morice *et al.* (2003)	57	3	Platinum + PTX	100 (57/57)	84 (48/57)	NR	51 (29/57)	Retrospective	[17]
Le *et al.* (2005)	61	3	CBDCA + PTX	100 (61/61)	80 (49/61)	54 (33/61)	26 (16/61)	Retrospective	[50]
Le *et al.* (2006)	58	3	CBDCA + PTX	100 (58/58)	79 (46/58)	55 (32/58)	28 (16/58)	Retrospective	[51]
Lee *et al.* (2006)	18	3	CDDP + PTX	100 (18/18)	78 (14/18)	NR	NR	Prospective	[20]
Tiersten *et al.* (2009)	58	3	CBDCA + PTX	62 (36/58)	NR	45 (26/58)†	NR	Prospective	[53]
Pölcher *et al.* (2009)	44	2	CBDCA + DTX	98 (43/44)	NR	73 (32/44)†	43 (19/44)†	Prospective	[35]
Pölcher *et al.* (2009)	44	3	CBDCA + DTX	91 (40/44)	NR	68 (30/44)†	27 (12/44)†	Prospective	[35]
Onda *et al.* (2009)	53	4	CBDCA + PTX	89 (47/53)	NR	72 (38/53)	55 (29/53)	Prospective	[27]
Vergote *et al.* (2010)	322	3	Platinum + taxane	91 (292/322)‡	NR	74 (239/322)‡	47 (152/322)‡	Prospective	[4]
Total Number	763			91 (695/763)	80 (193/242)	67 (430/640)	42 (288/687)		
Range	17–322	NAC 2–4 cycles		62–100	59–84	45–74	26–55%		

†Frequencies are recalculated to include all patients into denominators.
‡Frequencies are calculated from the number of patients in per-protocol analysis.
CBDCA: Carboplatin; CDDP: Cisplatin; DTX: Docetaxel; IDS: interval debulking surgery; NAC: Neoadjuvant chemotherapy; NR: Not recorded; PTX: Paclitaxel; RD: Residual disease.

with respect to the response to NAC (p = 0.82) and median survival (p = 0.74). The issue of whether women who received ≤three cycles of NACT benefited more than those who had >three cycles could not be answered in their study.

Colombo *et al.* analyzed prognostic factors in 61 patients treated with NACT in a retrospective study [16]. IDS was performed after three to six cycles of NAC consisting of platinum and PTX in 39 patients, and platinum and another agent in 22 patients. In addition to the response to NAC (p = 0.04), the range of mesenteric involvement (p = 0.025), performance of digestive resection (p = 0.01), residual tumor after IDS (p = 0.014) and number of NAC cycles (three or four vs >four; p = 0.04) were identified as statistically significant prognostic factors in univariate analysis. Median survival of patients treated with three or four cycles of NAC was much better than that of patients treated with >four cycles of NAC (31 vs 20 months, respectively).

Pölcher *et al.* prospectively compared two and three cycles of NAC in NACT, consisting of IDS and six cycles of combination regimen of CBDCA and docetaxel in total [35]. A total of 44 patients were each allocated to two or three cycles of the NAC arm. There were no significant differences in PFS (12.5 vs 12.2 months; p = 0.77) and OS (28.4 vs 24.1 months; p = 0.87). The authors concluded that a treatment schedule with two preoperative cycles is a reasonable option for NACT.

Bristow *et al.* demonstrated in their meta-analysis that each incremental increase in NAC cycles was associated with a 4.1-month decrease in MST (p = 0.046), and one of their important conclusions was that definitive operative intervention should be undertaken as early as possible in the treatment program [22]. On the contrary, Kang *et al.* demonstrated in their meta-analysis that the between-study variation of the number of NAC cycles did not influence survival (p = 0.701) [23]. The difference between the two studies probably results from differences in both selection of studies and statistical methods. In any case, we cannot draw a definitive conclusion from these meta-analyses.

From these aforementioned studies, it seems that three or four cycles may be the most likely optimal amount, and two cycles may be a reasonable option for the optimal number of NAC cycles. To decide the number of NAC cycles, individual evaluation of tumor resectability discussing in the following section may be of use. However, further evaluation is still necessary.

How can we predict successful debulking at primary or interval surgery?

In the early studies of NACT, selection of patients was based on the resectability of the tumors or patients characteristics at PDS, such as age, PS and medical conditions. Some investigators proposed criteria to predict successful or unsuccessful debulking. These methods may be also applicable in the setting of NACT to determine an indication or timing of IDS.

Nelson *et al.* defined several CT findings as unresectable disease and the results were compared with surgical outcome in 42 patients [36]. Successful cytoreduction (<2 cm residual disease) was accomplished in 23 out of 24 who fulfilled CT criteria for cytoreduction and six out of 18 with CT criteria predictive of inability to perform cytoreduction. They concluded that CT scan is an accurate method for predicting successful surgical cytoreduction. Dowdy *et al.* selected 17 CT findings and correlated with the possibility of optimal cytoreductive surgery (residual tumor <1 cm) in 87 patients [37]. A combination of diffuse peritoneal thickening and ascites was a most useful predictor of suboptimal cytoreduction and associated with a very low rate of optimal cytoreduction (32%). Qayyum *et al.* defined several imaging criteria for inoperable tumors and compared with operability at surgery in 137 patients [38]. Sensitivity and specificity for the prediction of suboptimal debulking were 76% (16 out of 21 patients) and 99% (115 out of 116 patients), respectively. They also found that CT and MRI were equally effective in the detection of inoperable tumor.

On the other hand, Vergote *et al.* utilized laparoscopic diagnosis to evaluate an operability in 77 patients [39]. In total, 79% of 28 patients, those supposed to be operable, were cytoreduced to <0.5 cm residual tumor. Deffieux *et al.* evaluated the role of laparoscopy in selecting candidates for complete cytoreduction surgery in 15 patients [40]. Among the 11 patients considered to have resectable tumors by laparoscopy, ten women had no macroscopic residual tumor after surgery. Fagotti *et al.* developed a scoring system based on laparoscopic evaluation of metastases in seven regions [41]. They demonstrated that this scoring system predicts suboptimal surgery with 100% sensitivity, 100% positive-predictive value and 74% accuracy.

Although these methods may be useful during the evaluation of resectability from the viewpoints of tumor spread, Aletti *et al.* pointed out the importance of patients' conditions and surgeons' expertise to achieve successful cytoreduction [42]. They found that patients' performance and surgeons' aggressive tendency are independently associated with optimal surgery in multivariate analysis. In another study, they identified a group of high-risk patients characterized by high tumor dissemination or stage IV, poor performance or nutritional status and age ≥75 years [43]. Aggressive debulking surgery was associated with morbidity of 63.6% and limited survival benefit in these patients.

Indication or timing of IDS should be evaluated, taking into account the patient's condition and the surgeon's expertise in addition to imaging diagnoses in clinical practice.

What is the optimal goal of IDS?

Most studies emphasized that the greatest advantage of NACT is a higher rate of optimal surgery in IDS. These studies uniformly used the same definition of optimal surgery in IDS as that in PDS. The meaning of residual disease after PDS and IDS is naturally different because chemoresistance may be altered by NAC and the planned number of postsurgical chemotherapy may be different. Thus, the definition of optimal surgery in IDS should be stricter than in PDS to indicate similar good survival from viewpoints of chemoresistance and remaining chemotherapy. In many retrospective studies and some prospective studies, a high proportion of optimal surgeries in IDS, based on the same definition, did not influence the survival of patients treated with NACT [4–6,9,12,15,16,20]. For example, Vrščaj *et al.* demonstrated higher optimal debulking in the IDS group compared with the PDS group (60 vs 22%, respectively; p = 0.001) but not improved survival (25 vs 26 months, respectively; p = not significant) [9]. Everett *et al.* reported similar observations of a higher proportion of optimal debulking in the IDS group than the PDS group (86 vs 54%, respectively; p < 0.001), but comparable survival (33 vs 42 months, respectively; p = not significant) [12]. Lee *et al.* presented an improved rate of optimal surgery (78% for IDS vs 46% for PDS; p = 0.04) without improving survival (53 months for IDS vs 55 months for PDS; p = not significant) [20]. These results support our idea.

As far as we know, there have been few studies addressing the definition of optimal surgery for IDS during NACT. Although it was not a direct analysis, we related the size of the residual tumor and survival after interval look or debulking surgery during PDS-CT based on the assumption that chemotherapy after interval surgery is identical between NACT and PDS-CT [48]. Interval look and debulking surgeries were performed after three or four cycles of chemotherapy for patients with optimal and suboptimal PDS, respectively. The 5-year survival of patients with no residual tumor after interval surgery was comparable with that of patients with minimal residual tumor (<2 cm) after PDS (47 vs 40%, respectively), while the 5-year survival of patients with minimal residual tumor after interval surgery is much worse (0%). Colombo *et al.* analyzed the prognostic factors in patients treated with NACT. They found that the size of the residual tumor is a significant prognostic factor (p = 0.014), and the 5-year survival of patients with no residual tumor, <1 cm tumor or >1 cm tumor was 33, 11 or 0%, respectively [16]. Mazzeo *et al.* reported similar results among patients treated with NACT [49]. The median survival of patients with no residual tumor at IDS is significantly better than that of patients with any residual tumor (41 vs 23 months, respectively; p = 0.0062). Almost 50% of patients with no residual tumor survived for 4 years, whereas no patients with residual tumor survived longer than 4 years. For long-term survival, surgery leaving even minimal residual tumor is not optimal.

Pölcher *et al.* addressed the definition of optimal surgery at IDS [35]. They performed a multivariate analysis of prognostic factors and found that no residual tumor was independently associated with good survival (hazard ratio: 0.33; p < 0.001).

They stated that optimal debulking after NAC should be defined as no gross residual disease. Although this suggestion may be based on a somewhat aggressive standpoint, it also supports our opinion. Without addressing the definition of optimal debulking, Kuhn *et al.* also demonstrated by multivariate analysis (relative risk: 14.3; p = 0.02) [18] and Schwartz *et al.* demonstrated by univariate analysis (p < 0.001) that macroscopic residual tumor is a significantly worse prognostic factor for OS [7]. Le *et al.* [50] and Le *et al.* [51] demonstrated a significant association between macroscopic residual tumor and PFS by multivariate analysis (p = 0.003 and 0.04, respectively). All of these studies support our opinion from an aggressive standpoint.

On the basis of these studies, we can say that the definition of optimal debulking in IDS should be stricter than in PDS and that the definition should be no residual tumor in IDS, even though the definition of optimal surgery in PDS remains <1-cm residual tumors.

How frequently can we achieve optimal IDS following NAC with platinum and taxane?

Bristow *et al.* [22] and Kang *et al.* [23] reported that the weighted mean rate of optimal debulking was 65.0 and 70.0%, respectively, in their meta-analyses. Regrettably, these results may not be in accordance with current clinical practice. For example, these studies used the definition of optimal surgery as defined for each cohort, which is, in the majority of cases, residual tumors of <2 cm. In addition, these studies include cohorts treated with NAC regimens other than platinum–taxane combinations. Table 6 summarizes the performance rate and results of IDS among cohorts treated with a NAC regimen composed of platinum and taxane [4,17,18,20,27,35,50–53].

The median performance rate of IDS after three or four cycles of NAC ranged from 62 to 100% in each cohort base, and the average performance rate was 91% (695 out of 763). IDS resulted in residual disease with <2 cm residual tumors (i.e., the older definition of optimal surgery) in 80% (193 out of 242) of patients (range: 59–84% in each cohort base). Similarly, IDS resulted in residual disease with <1 cm residual tumors (i.e., present definition of optimal surgery) in 67% (430 out of 640) of patients (range: 45–74% in each cohort base). Finally, complete resection of all tumors (i.e., recommended definition of optimal surgery) was achieved in 42% (288 out of 687) of patients (range: 26–55% in each cohort base). Although these cohorts still include various selection criteria for NACT, different decision criteria for performing IDS and different target goals for surgery, as well as include retrospective studies, this information may be useful in order to predict an ordinary course of treatment.

As an average course of NACT for advanced-stage ovarian cancer by using a standard platinum–taxane combination regimen, IDS is possible in approximately 91% of patients, optimal debulking according to the present definition (<1 cm residual tumor) is possible in approximately 67% of patients, and complete resection can be achieved in approximately 42% of patients.

Should we exclude patients with clear-cell or mucinous histology from NACT?

One of the important questions is whether we should avoid performing NACT for advanced-stage ovarian cancer with chemoresistant histology, such as clear-cell or mucinous adenocarcinoma. In principle, NACT does not seem beneficial for patients with chemoresistant histology. Current publications seldom discuss differences in histology.

Inciura *et al.* reported on a retrospective, comparative study between NACT (n = 213) and PDS-CT (n = 361) [13]. The number of patients with serous, mucinous, endometrioid, and other types were 84, 48, 49 and 32, respectively, in the NACT group and 135, 67, 118 and 41, respectively, in the PDS-CT group. There was no statistical difference in OS between NACT and PDS-CT in serous (p = 0.396), endometrioid (p = 0.197) and mucinous (p = 0.256) histology. We can find no apparent demerits of NACT for patients with mucinous adenocarcinoma in this study.

Ongoing Phase III studies [24,25] and a recently published EORTC study [4] set the criteria for tumor marker CA125 and CEA in eligibility. These criteria may work not only to exclude the malignancy of digestive tracts but also to decrease the enrollment of patients with clear-cell adenocarcinoma or mucinous histology. Actually, patients with clear-cell adenocarcinoma or mucinous adenocarcinoma enrolled in the EORTC study was only 4.3% (29 out of 670).

Accumulation of data may be necessary in order to determine whether we should avoid selecting NACT for patients with clear-cell adenocarcinoma or mucinous adenocarcinoma, although, in principle, NACT would not seem beneficial for patients with such chemoresistant histology.

Expert commentary

When NACT was an alternative treatment for patients with advanced ovarian, tubal, or peritoneal cancer, selection of patients with primarily unresectable tumors was one of most important issues before initiating treatment. For this purpose, some investigators proposed the criteria of unresectablity using CT or MRI results [36–38], while others used or recommended diagnostic laparoscopy [39–41] to select such patients, as previously mentioned. Now that NACT is a standard treatment option, the roles of these criteria may change. How to diagnose ovarian, tubal or peritoneal malignancy and diagnose the advanced stage of these diseases (i.e., diagnose as adequate disease for NACT) without wasting time is a very important issue before starting NACT. As discussed previously, cytology may be a useful tool for this purpose. Although we cannot diagnose all patients with ovarian, tubal or peritoneal cancer correctly by cytological diagnosis alone, we can correctly select patients with these diseases by cytology in combination with imaging diagnosis and serum tumor markers. However, it is noteworthy that malignancies of other origins, such as breast and digestive tract, were carefully ruled out by some other criteria in the setting of clinical study. Similar careful diagnosis is necessary to use cytological diagnosis at clinical practice.

Once again, when NACT was an alternative treatment for patients with more advanced-stage ovarian, tubal or peritoneal cancer with primarily unresectable tumors, achievement of optimal surgery with <1 cm residual tumors in IDS might have been very positive because the prognoses of these patients were deemed to be poor. Now that NACT is a standard treatment option for all patients with stage III/IV, NACT should be selected with the expectation of the best outcomes for patients. We should perform IDS in NACT with the aim of complete resection of all macroscopic tumors, taking into consideration that leaving even minimal residual disease makes prognoses of the patients poor.

Along with the change in the role of NACT, we should also change the management of patients regarding diagnosis before treatment and IDS.

Five-year view

Mature, long-term, follow-up results from all or most of the ongoing Phase III studies will probably be available in order to help establish a role for NACT. The role of NACT itself and new strategies of chemotherapy in NACT will be a focus of research. In the setting of PDS-CT, the strategies of intraperitoneal (IP) chemotherapy; a combination regimen of CBDCA and dose-dense, weekly PTX; and a combination of molecular-target therapy, are candidates for replacing an intravenous, tri-weekly combination of platinum and taxane based on the results of Phase III studies [54–56]. All of these strategies can be combined with NACT, and several studies of these treatments have been performed or are in progress.

The Southwest Oncology Group (SWOG) performed a Phase II study of NAC and IDS followed by intravenous/IP chemotherapy in women with stage III/IV ovarian, tubal or peritoneal cancer with bulky disease [53]. NAC consisted of three cycles of intravenous CBDCA and PTX. Postsurgical chemotherapy for optimally cytoreduced patients consisted of six cycles of intravenous and IP PTX and IP CBDCA. In total, 26 out of 58 enrolled patients underwent optimal IDS and received postsurgical intravenous/IP chemotherapy. PFS and OS for 26 patients who received intravenous/IP chemotherapy is 29 and 34 months, respectively. They concluded that these results compare favorably with other studies of suboptimally debulked patients and that randomized comparisons are necessary to make conclusions regarding the toxicity and efficacy of their intravenous/IP regimen. The University Health Network in Canada started a Phase I/II study of NAC and IDS followed by IP CDDP and intravenous PTX in February 2007 (ClinicalTrials.gov identifier: NCT00889733 [101]). The Clinical Trial Group of the National Cancer Institute of Canada also started a randomized Phase II/III study in September 2009 to compare three post-IDS chemotherapy arms, including an intravenous PTX and intravenous CBDCA arm, intravenous/IP PTX and IP CDDP arm, and intravenous/IP PTX and IP CBDCA arm (ClinicalTrials.gov identifier: NCT00993655 [101]).

Pölcher *et al.* performed a Phase II study of NACT using a molecular target agent to assess activity and tolerability [57]. The regimen was a combination therapy of tri-weekly CBDCA and PTX with the multi-target, tyrosine kinase inhibitor, sorafenib (400 mg twice daily). The planned protocol treatment was two cycles of NAC and IDS followed by four cycles of postsurgical chemotherapy and maintenance, single-agent oral sorafenib through 1 year. Unfortunately, the study was terminated early because all four enrolled patients suffered severe toxicities after NAC and IDS. Although the regimen was not feasible, the authors conclude that further evaluations of sorafenib are warranted. Wright *et al.* initiated a Phase II study of neoadjuvant CBDCA, PTX and bevacizumab in May 2010 (ClinicalTrials.gov identifier: NCT01146795 [101]). The treatment schedule includes three cycles of NAC and IDS followed by six cycles of postsurgical chemotherapy.

The new strategies of NACT using a wide variety of schedules or agents will be assessed for efficacy and toxicity with great enthusiasm. It is expected that such strategies will contribute to further improvements in the outcome of patients with advanced ovarian, tubal or peritoneal cancer.

Key issues

- Retrospective or nonrandomized prospective studies demonstrated that neoadjuvant chemotherapy-setting treatment (NACT) seemed to greatly reduce surgical invasiveness without compromising the survival of patients with advanced ovarian, tubal or peritoneal cancer.
- NACT is expected to become a standard treatment for unselected patients with advanced ovarian cancer when favorable results are confirmed by Phase III studies and several problems are resolved.
- Cytological examination of ascites, pleural effusion or tumor, in addition to imaging diagnosis and tumor markers, may be necessary before NACT can be used for accurate diagnosis of target diseases, unless we select diagnostic laparotomy or laparoscopy.
- Although further evaluation is necessary, three or four cycles may be the most likely optimal amount, and two cycles may be a reasonable option for the optimal number of neoadjuvant chemotherapy cycles.
- The definition of optimal debulking in interval debulking surgery should be stricter than in primary debulking surgery and it should mean no residual tumor, even though the definition in primary debulking surgery remains <1-cm residual tumors.
- As an average course of NACT for advanced ovarian cancer by using a standard platinum–taxane combination regimen, interval debulking surgery is possible in approximately 91% of patients, optimal debulking (<1-cm residual tumor) is possible in approximately 67% of patients, and complete resection can be achieved in approximately 42% of patients.
- Accumulation of data may be necessary in order to determine whether we should avoid selecting NACT for patients with chemoresistant histology, such as clear-cell adenocarcinoma or mucinous adenocarcinoma.

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The History of the Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG)

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The Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG) was organized in 1994. The GCSG has developed under the leadership of three successive group representatives, five principal study investigators, the cooperation of group members and the support of several public research funds. At present, 38 institutions are participating as active members of the GCSG of the JCOG. In addition to gynecologic oncologists, medical oncologists, pathologists and radiotherapists are participating in our group. Our group manages female genital malignancies including uterine cervical, endometrial, ovarian, tubal and vulvar cancers. Because the incidences of uterine cervical (in younger women), endometrial and ovarian cancer have increased in Japan in recent years, we are developing new standard treatments especially for these malignancies. As of 31 May 2011, our group has conducted six JCOG clinical trials (three completed and three ongoing) and completed one JCOG accompanying study, which is now in preparation for publication. Our group has also conducted several retrospective studies, and Phase I and II trials independent of the JCOG Data Center. Our aim is to conduct unique and high-quality clinical trials which we can appeal to the world. In this review, we present the organization and achievements of our group, along with a list of participating institutions, as the history of the GCSG of the JCOG.

Key words: gynecologic cancer – treatment – clinical trial

ORGANIZATION OF THE GYNECOLOGIC CANCER STUDY GROUP OF THE JAPAN CLINICAL ONCOLOGY GROUP

The Gynecologic Cancer Study Group (GCSG) of the Japan Clinical Oncology Group (JCOG) was organized in 1994 with Dr Ryuichiro Tsunematsu as the first group representative. The original members of the GCSG were also members of a study group called 'A Study for the efficacy of dose-intensive chemotherapy for advanced ovarian cancer', which was organized by Dr Tsunematsu as the principal investigator with the support of Grants-in-Aid for Cancer Research from the Ministry of Health and Welfare during the 1994–97 fiscal years. This group was taken over by a study group organized by Dr Hiroyuki Yoshikawa entitled 'A study for the development of new treatment methods for gynecologic malignancy', which was supported by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare (MHLW) during the 1998–2001 fiscal years. In 1998, the group representative of the GCSG of JCOG was handed over to Dr Yoshikawa from Dr Tsunematsu. In 2001, a new study group called 'A study for the multidisciplinary treatment aiming to improve the prognosis of advanced ovarian cancer' was organized by Dr Yoshikawa with the support of Health Sciences Research Grants for Clinical Research from the MHLW during the 2001–03 fiscal years. After 2004, this study group headed by Dr Yoshikawa was renamed 'A study for the multidisciplinary treatment for advanced ovarian cancer' for the

2004–06 fiscal years, followed by 'A study for the establishment of the treatment starting with neoadjuvant chemotherapy for advanced ovarian cancer' for the 2007–09 fiscal years, and is now called 'A study to prove the treatment starting with neoadjuvant chemotherapy as standard treatment for advanced ovarian cancer'. Going back to 2002, the study group supported by Grants-in-Aid for Cancer Research was taken over by Dr Toshiharu Kamura with the same study name for the fiscal years 2002–05. Subsequently in 2003, a new study group called 'A study for the establishment of standard chemotherapy in the multidisciplinary treatment aiming to improve the prognosis of uterine cervical cancer' was organized by Dr Kamura with the support of Health Sciences Research Grants for Clinical Research from the MHLW during the 2003–05 fiscal years. Dr Kamura took over as the group representative of GCSG of JCOG from Dr Yoshikawa in 2005 and is still in charge. The chief investigator of the study group supported by Grants-in-Aid for Cancer Research was changed to Dr Ikuo Konishi from Dr Kamura while retaining the same study name for the 2006–09 fiscal years, and the study group organized by Dr Kamura supported by Health Sciences Research Grants for Clinical Research was renewed as a study group called 'A study for the establishment of standard treatment for advanced or recurrent uterine cervical cancer' for the 2006–08 fiscal years. Both study groups completed their respective studies at the ends of their planned periods. In 2010, Dr Takahiro Kasamatsu organized a study group called 'A study for the establishment of the standard treatment for rare cancers among gynecological malignancy' supported by Grants-in-Aid for Cancer Research and Development from the Ministry of Health, Labor and Welfare for the 2010 fiscal year. Meanwhile, some members of the GCSG participated in the study called 'A multi institutional cooperative study for the establishment of the standard treatment for hyper responsive malignancy' organized by Dr Tomomitsu Hotta for the 2005–07 fiscal years and by Dr Kensei Tobinai for the 2008–11 fiscal years; both these were supported by Grants-in-Aid for Cancer Research for the 2005–09 fiscal years or by Grants-in Aid for Cancer Research and Development for the 2010–11 fiscal years from the MHLW.

At present, the GCSG of the JCOG consists of 38 institutions, mainly university hospitals and cancer center hospitals. In addition to gynecologic oncologists, medical oncologists, pathologists and radiotherapists are also participating in the GCSG.

TREATMENT MODALITIES FOR GYNECOLOGICAL MALIGNANCIES AND TARGET DISEASES FOR CLINICAL TRIALS

In contrast to other malignancies, surgery and radiotherapy used to be the gold standards for the treatment of gynecological malignancies. However, since the late 1970s, many anticancer drugs have been developed; some of which are effective on gynecological malignancies. Therefore, at present, in addition to surgery and radiotherapy, chemotherapy has occupied an important position in treatment. Although the prognosis of those who have gynecologic malignancies has recently been substantially improved by combining these modalities, it is still not satisfactory for some diseases. Therefore, the GCSG has conducted clinical trials to develop more effective standard treatments. Our group covers female genital malignancies including uterine cervical, endometrial, ovarian, tubal and vulvar cancers. Because the incidences of uterine cervical (in younger women), endometrial and ovarian cancer have increased rapidly in Japan in recent years, we have continued developing new standard treatments especially for these malignancies.

ACHIEVEMENTS OF THE GCSG OF THE JCOG

As of 31 May 2011, the GCSG has conducted six JCOG clinical trials (three completed and three ongoing) and completed one JCOG accompanying study, which is now in preparation for publication. Our group also conducted several retrospective studies as well as Phase I and II trials independent of the JCOG Data Center. Here, we present the main findings of our studies.

Ovarian Cancer

JCOG9412: Phase II Study of Dose-intensive Cyclophosphamide, Doxorubicin and Cisplatin with Granulocyte Colony-stimulating Factor in Patients with Advanced Epithelial Ovarian Cancer (1)

We conducted a Phase II study of dose-intensive cyclophosphamide, doxorubicin and cisplatin (CAP; 750 mg/m^2 cyclophosphamide, 55 mg/m^2 doxorubicin and 75 mg/m^2 cisplatin) for patients with Stage III–IV suboptimally debulked ovarian cancer. The aim of this study was to assess the safety and evaluate the antitumor activity (i.e. pathological complete response) of this regimen by using second-look laparotomy. After the primary surgery, patients with residual disease ($\geq$1 cm) were treated with dose-intensive CAP every 3 weeks for six courses. Granulocyte colony-stimulating factor was administered from day 3 at 2 μg/kg. A pathological complete response (CR) rate at the time of planned interim analysis was observed in more than 4 (the lower cut-off point) of 28 patients. In December 1996, the projected accrual was closed in order to enroll 70 patients totally. Major toxicity was Grade 4 neutropenia (76.5%) accompanied by Grade 3 neutropenic fever (8.3%) at the latest monitoring. No treatment-related deaths occurred, and no Grade 3 or 4 neurological toxicity was observed. The toxicity of this treatment was considered to be tolerable.

This study is our first JCOG study, which was started in 1994. The results were presented at the 6th Biennial Meeting of the International Gynecologic Cancer Society held in Fukuoka, Japan, in 1997.

JCOG0206: Feasibility Study of Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery for Stage III/IV Ovarian, Tubal and Peritoneal Cancers (2,3)

We performed this feasibility study 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 to determine whether we can omit diagnostic surgical procedures before the initiation of treatment. Eligible patients were presumed to have 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 IDS and an additional four cycles of chemotherapy. The primary endpoint was the proportion of clinical complete remission (cCR) among Stage III/IV müllerian carcinomas. The major secondary endpoint was the positive predictive value (PPV) of clinical diagnosis. Fifty-six patients were enrolled into the study between January 2003 and February 2004. The PPV of overall clinical diagnosis for the tumor origin, histology and stage was 95% (53/56). Fifty-three patients received the protocol treatment and 22 (42%) achieved cCR. The median overall and progression-free survival (PFS) was 45 and 14 months, respectively. NAC without diagnostic laparoscopy for advanced müllerian carcinomas seemed to hold sufficient promise to be compared with upfront surgery in a Phase III trial. We proceeded to Phase III studies, which are presented later (JCOG0602).

JCOG0503: Phase II Trial of Oral Etoposide and Intravenous Irinotecan for Patients with Platinum-resistant and Taxane-pre-treated Ovarian Cancer (4)

We started this study because effective chemotherapy for patients with platinum-resistant ovarian cancer is currently an unmet medical need. Oral etoposide and intravenous irinotecan as monotherapies have demonstrated some efficacy for platinum-resistant ovarian cancer. Thus, combining these two topoisomerase inhibitors is an intriguing idea. After Phase I and feasibility studies, we began a nationwide Phase II study to evaluate the safety and efficacy of this regimen for patients with platinum-resistant and taxane-pre-treated ovarian, tubal and peritoneal cancers. Eligible patients were given etoposide at 50 mg/m^2 p.o. from days 1–21 and irinotecan 70 mg/m^2 i.v. at days 1 and 15; this was repeated every 28 days for up to six cycles. The primary endpoint was response rate; the secondary endpoints were adverse events, PFS and overall survival (OS). The expected and threshold values for the primary endpoint were set at 35 and 20%, respectively. Sixty patients are to be registered from April 2009 to March 2011 in the initial plan. The study period was extended, and 42 patients were registered as of 16 May 2011. This study is currently ongoing.

JCOG0602: Phase III Trial of Upfront Debulking Surgery Versus NAC for Stage III/IV Ovarian, Tubal and Peritoneal Cancers (5)

Based on the promising results of NAC in our previous study (JCOG0206), we have been performing a Phase III study of treatment starting with NAC versus standard treatment starting with primary debulking surgery (PDS) for Stage III/IV müllerian carcinomas since November 2006. The purposes of this study are to prove the non-inferiority of the efficacy of treatment starting with NAC and to demonstrate the decrease in adverse effects and reduced invasiveness. Three hundred patients will be randomized over 3 years according to the initial plan. NAC arm patients undergo four cycles of NAC with paclitaxel plus carboplatin followed by IDS and an additional four cycles of post-surgical chemotherapy. Standard arm patients undergo PDS and eight cycles of post-surgical chemotherapy with or without IDS. The primary endpoint is OS. The major secondary endpoints are the incidence of adverse events and parameters representing surgical invasiveness. The study period was extended, and 285 patients were registered as of 16 May 2011. The study is currently ongoing.

Multicenter Retrospective Study for Prognostic Factors of Stage IV Epithelial Ovarian Cancer (6)

We conducted a multicenter retrospective analysis to elucidate the prognostic factors of Stage IV epithelial ovarian cancer (EOC). The data for all patients with Stage IV EOC that was surgically confirmed and initially treated in each institution between January 1990 and December 1997 were collected from 24 member institutions of the GCSG in November 1999. In total, 275 patients with Stage IV ovarian cancer were identified. The most common site of the extraperitoneal disease was malignant pleural effusion (39.6%). Of the 225 patients who underwent an attempt at surgical debulking, 70 (31.1%) were optimally cytoreduced. Most patients received platinum-based combination chemotherapy for primary chemotherapy. In multivariate analysis, performance status, histology and residual disease after cytoreductive surgery were independent prognostic predictors of outcomes. The overall median survival for optimally debulked patients was 32 months compared with 16 months for suboptimally debulked patients ($P < 0.0001$; hazard ratio, 0.415). Optimal surgical debulking, performance status and histology appeared to be important prognostic factors of survival in patients with Stage IV EOC.

Multicenter Phase I Study of Chemotherapy Consisting of Cisplatin, Paclitaxel and Escalating Doses of Doxorubicin in Advanced Ovarian Cancer (7)

We designed a Phase I/II study in patients with advanced ovarian cancer (AOC) for first-line chemotherapy using a combination of a fixed dose of cisplatin and paclitaxel, which was the standard regimen at that time, with escalating doses of

doxorubicin, which has been shown to have favorable effects on AOC according to a meta-analysis, given at every 3 weeks. Eligible patients had Stage III or IV ovarian cancer. Dose-limiting toxicity (DLT) was defined as prolonged Grade 4 neutropenia, febrile neutropenia or non-hematologic toxicity ≥Grade 3. Four different dose levels were planned. The dose of doxorubicin was escalated from 20 to 50 mg/m^2 in sequential cohorts, and fixed doses of 75 mg/m^2 cisplatin and 110 mg/m^2 paclitaxel in a 24 h infusion were tested. Between December 1998 and December 2000, 28 patients entered the study. The patients received a mean of 5.4 courses. Non-hematologic toxicity was generally mild, except for Grade 3 vomiting. No Grade 3 neurotoxicity was observed. Hematologic toxicities were Grade 3–4 neutropenia in all patients and Grade 3 anemia in 44% patients. At Level IV, two of six patients developed DLT that manifested as febrile neutropenia in two and diarrhea in one. Clinical response was observed in 17 of evaluable patients (89%). The recommended dose was at Level IV with 50 mg/m^2 doxorubicin. Further studies including anthracyclines for first-line chemotherapy of ovarian cancer are warranted because of its favorable antitumor activity.

Multicenter Retrospective Study for Fertility-sparing Surgery for Stage I EOC (8)

The objective of this study was to assess the clinical outcomes and fertility in patients treated conservatively for unilateral Stage I invasive EOC. A multi-institutional retrospective investigation was undertaken to identify patients with unilateral Stage I EOC treated with fertility-sparing surgery. Favorable histology was defined as Grade 1 or 2 adenocarcinoma excluding clear cell histology. A total of 211 patients treated between 1985 and 2004 were identified from 30 institutions. The median follow-up duration was 78 months. Five-year OS and recurrence-free survival were 10 and 97.8%, respectively, for Stage IA and favorable histology (n = 108); 100 and 100%, respectively, for Stage IA and clear cell histology (n = 15); 100 and 33.3%, respectively, for Stage IA and Grade 3 (n = 3); 96.9 and 92.1%, respectively, for Stage IC and favorable histology (n = 67); 93.3 and 66.0%, respectively, for Stage IC and clear cell histology (n = 15); and 66.7 and 66.7%, respectively, for Stage IC and Grade 3 (n = 3). Forty-five (53.6%) of 84 patients who were nulliparous at surgery and married at the time of investigation gave birth to 56 healthy children. Our data confirm that fertility-sparing surgery is a safe treatment for Stage IA patients with favorable histology and suggest that Stage IA patients with clear cell histology and Stage IC patients with favorable histology could be candidates for fertility-sparing surgery followed by adjuvant chemotherapy.

Cervical Cancer

JCOG0102: Phase III Randomized Trial of NAC Followed by Radical Hysterectomy Versus Radical Hysterectomy for Bulky Stage I/II Cervical Cancer (9,10)

We compared NAC followed by radical hysterectomy (RH) with RH for bulky Stage I/II cervical cancer. Patients with Stage IB2, IIA (>4 cm), or IIB squamous cell carcinoma of the uterine cervix were randomly assigned to receive either BOMP (7 mg bleomycin from days 1 to 5, 0.7 mg/m^2 vincristine on day 5, 7 mg/m^2 mitomycin on day 5 and 14 mg/m^2 cisplatin from days 1 to 5) q21 days for two to four cycles followed by RH (NAC arm) or undergo RH (RH arm). Patients with positive surgical margins, metastatic nodes, parametrial involvement and/or deep stromal invasion received post-operative irradiation. The primary endpoint was OS. Totally, 134 patients (67 NAC and 67 RH) were randomized between December 2001 and August 2005. The first planned interim analysis was performed in July 2005 using data from 108 patients registered as of November 2004. We are now preparing to publish the results of the interim analysis and the final analysis.

JCOG0505: Phase III Trial of Paclitaxel plus Carboplatin Versus Paclitaxel plus Cisplatin in Stage IVB, Persistent or Recurrent Cervical Cancer (11)

Paclitaxel and cisplatin is the standard regimen for treating patients with Stage IVB, persistent or recurrent cervical cancer who are not amenable to curative treatment with local therapy. However, carboplatin is expected to be more feasible than cisplatin in terms of effectiveness and toxicity management. Therefore, the aim of this randomized trial was to compare the efficacy of paclitaxel and carboplatin (TC) with that of paclitaxel and cisplatin (TP) as a control. This trial was designed to evaluate the non-inferiority of TC compared with TP. The primary endpoint is OS. The secondary endpoints are PFS, response rates, adverse events, severe adverse events and the proportion of non-hospitalization periods compared with planned treatment periods served as an indicator of quality of life. Planned accrual was completed in November 2011. Follow-up data are now being accumulated.

JCOG0806A: Multicenter Retrospective Study for Clinical and Pathological Analyses for Stage IB1 Small (<2 cm) Uterine Cervical Cancer

This study has been performed as JCOG accompanying study since 2008. The study was designed to reveal clinical outcomes and pathological findings of Stage IB1 uterine cervical cancer. Final reports of the results were issued by the data center of JCOG in August 2010. We are now preparing to publish the results as well as for a prospective study to prove the efficacy of less-invasive surgery for patients with Stage IB1 small (<2 cm) uterine cervical cancer.

Multicenter Retrospective Study for Pulmonary Metastasectomy for Uterine Cervical Cancer (12)

This study evaluated the results of the resection of pulmonary metastases from cervical cancer. Among 7748 patients with primary Stage IB or II cervical cancer who underwent curative initial treatment consisting of radical hysterectomy

or radiotherapy in 22 hospitals, pulmonary metastases detected after a disease-free period were resected from 29 (0.37%) patients with the intention to cure by 30 June 1998. The 5-year disease-free survival rate (DFS) after pulmonary metastasectomy for all patients was 32.9%. Patients with one or two pulmonary metastases had a 5-year DFS of 42.2% compared with 0% for patients with three or four metastases ($P = 0.0003$). Patients with squamous cell cancers (SCC) had a 5-year DFS of 47.4% compared with 0% for patients with adenosquamous cell cancers or adenocarcinoma ($P = 0.0141$). In multivariate analysis, the significant prognostic variables for DFS were less than or equal to two metastases ($P = 0.0232$) and SCC ($P = 0.0168$). Cervical cancer patients with pulmonary metastases after successful initial treatment can be expected to achieve long-term DFS by pulmonary metastasectomy when there are less than or equal to two metastases and the histology is SCC.

Endometrial cancer

Multicenter Retrospective Study for Conservative Therapy for Endometrioid Adenocarcinoma and Atypical Endometrial Hyperplasia of the Endometrium in Young Women (13)

Thirty-nine patients with endometrioid adenocarcinoma (EA) and atypical endometrial hyperplasia (AH) of the endometrium who received conservative treatment to preserve fertility were collected from member institutions of the GCSG. The institutional diagnosis of EA in 29 patients was changed to AH in 10, complex hyperplasia in 3 and atypical polypoid adenomyoma in 3; the diagnosis of AH in 10 patients was changed to EA in 1 and simple hyperplasia in 1 by a central pathological review. Nine of 12 women (75%) with EA and 15 of 18 women (83%) with AH had initially responded to medroxyprogesterone acetate (MPA) treatment. Two of nine responders with EA later developed relapse and one of them had a lymph node metastasis. Two became pregnant and one delivered one full-term infant. One of the responders with AH had a relapse in the endometrium. Five became pregnant and four delivered four normal infants. Young women with EA localized in the endometrium who wish to preserve their fertility may be treated as successfully with MPA as those with AH. Based on the results, we conducted the Phase II study presented below.

Multicenter Phase II Study of Fertility-sparing Treatment with MPA for EA and AH in Young Women (14)

This multicenter prospective study was carried out at 16 institutions to assess the efficacy of fertility-sparing treatment using MPA for EA and AH in young women. Twenty-eight patients presumed to have Stage IA EA and 17 patients with AH who were <40 years of age were enrolled. All patients were given a daily oral dose of 600 mg MPA with low-dose aspirin. This treatment continued for 26 weeks as long as the patients responded. Either estrogen–progestin therapy or fertility treatment was provided for the responders after MPA therapy. The primary endpoint was a pathological CR rate. Toxicity, pregnancy rate and PFS were the secondary endpoints. CR was found in 55% of EA cases and 82% of AH cases; the overall CR rate was 67%. Neither therapeutic death nor irreversible toxicities were observed. During the 3-year follow-up period, 12 pregnancies and 7 normal deliveries were achieved after MPA therapy. Fourteen recurrences were found in 30 patients (47%) between 7 and 36 months. The efficacy of fertility-sparing treatment with a high dose of MPA for EA and AH was proven by this prospective trial. However, even in responders, close follow-up is required because of the substantial rate of recurrence.

FUTURE PERSPECTIVES OF THE GCSG OF THE JCOG

We are now planning to conduct several studies such as less invasive surgery for Stage IB1 uterine cervical cancer, maintenance chemotherapy following concurrent chemoradiotherapy for locally advanced uterine cervical cancer and chemotherapy for uterine leiomyosarcoma. So far, we have not had an opportunity to collaborate with foreign societies. However, in the future, we would like to make a protocol that interests foreign societies. We hope that the GCSG will develop better treatments for women who suffer from gynecologic cancer via unique and high-quality clinical trials.

PARTICIPATING INSTITUTIONS (AS OF 31 MAY 2011)

Hokkaido University, Sapporo Medical University, Iwate Medical University, Tohoku University, University of Tsukuba, National Defense Medical College, Saitama Cancer Center, Saitama Medical Center, The Jikei University Kashiwa Hospital, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, The Jikei University School of Medicine, Cancer Institute Hospital, The University of Tokyo, Juntendo University, NTT Medical Center Tokyo, Kitasato University, Niigata Cancer Center Hospital, Shinshu University, Aichi Cancer Center, Nagoya University, Kyoto University, Osaka City University, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka City General Hospital, Sakai Hospital Kinki University Faculty of medicine, Hyogo Cancer Center, Tottori University, National Hospital Organization Kure Medical Center, National Hospital Organization Shikoku Cancer Center, National Hospital Organization Kyushu Cancer Center, Kurume University, Kyushu University, Saga University, Kumamoto University, Kagoshima City Hospital and University of the Ryukyus.

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Conflict of interest statement

None declared.

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