European Journal of Cancer 130 (2020) 114–125

Available online at www.sciencedirect.com

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Clinical Trial

Comparison of survival between primary debulking surgery and neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomised trial

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Received 2 August 2019; received in revised form 5 February 2020; accepted 9 February 2020

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https://doi.org/10.1016/j.ejca.2020.02.020

KEYWORDS
Ovarian neoplasms;
Neoadjuvant chemotherapy;
Interval debulking surgery;
Primary debulking surgery

Abstract ***Background:*** Regarding the comparison between primary debulking surgery (PDS) and neoadjuvant chemotherapy (NACT) for stage III/IV ovarian, tubal and peritoneal cancers, EORTC55971 and CHORUS studies demonstrated noninferiority of NACT. Previously, we reported reduced invasiveness of NACT in JCOG0602. This is a final analysis including the primary endpoint of overall survival (OS).
Methods: Patients were randomised to PDS (PDS followed by 8x paclitaxel and carboplatin, i.e. TC regimen) or NACT (4x TC, interval debulking surgery [IDS], 4x TC). The primary endpoint was OS. The noninferiority hazard ratio (HR) margin for NACT compared with PDS was 1·161. The planned sample size was 300.
Findings: Between 2006 and 2011, 301 patients were randomised, 149 to PDS and 152 to NACT. The median OS was 49·0 and 44·3 months in the PDS and NACT. HR for NACT was 1·052 [90·8% confidence interval (CI) 0·835–1·326], and one-sided noninferiority *p*-value was 0·24. Median progression-free survival was 15·1 and 16·4 months in the PDS and NACT (HR: 0·96 [95%CI 0·75–1·23]). In the PDS arm, 147/149 underwent PDS and 49/147 underwent IDS. In the NACT arm 130/152 underwent IDS. Complete resection was achieved in 12% (17/147) of PDS and 31% (45/147) of PDS ± IDS in the PDS arm and in 64% (83/130) of IDS in the NACT arm. Optimal surgery (residual tumour <1 cm) was achieved in 37% (55/147), 63% (92/147), and 82% (107/130 respectively. In the NACT, PS 2/3, serum albumin ≤2·5, CA125 > 2000 an institution with low study activity was advantageous, whereas clear/mucinous histology was disadvantageous for OS.
Interpretation: The noninferiority of NACT was not confirmed. NACT may not always be a substitute for PDS. However, as our study had smaller numbers, the noninferiority of the previous studies cannot be denied.
Funding: Ministry of Health, Labour and Welfare, Japan and the National Cancer Center, Japan.
Clinical trial information: UMIN000000523.

1. Introduction

Epithelial ovarian, tubal, or peritoneal cancer is acknowledged to have the worst prognosis among major gynecologic malignancies. One of the reasons for this is that most cases present in advanced stages (about two-thirds at stage III/IV [1]). The prognosis of advanced disease is very poor, with 5-year survival rates lower than 35% [1]. The standard treatment for advanced tumours is primary debulking surgery (PDS), followed by platinum and taxane chemotherapy. Although optimal debulking (less than 1 cm in maximum diameter of residual tumour) or complete resection (no residual tumour) is desirable, optimal surgery is only achieved in 25%–40% of cases undergoing PDS in the vast majority of institutions [2].

Patients with apparently unresectable tumours by imaging study or laparoscopic inspection and patients with low performance status (PS) or medical complications often receive neoadjuvant chemotherapy (NACT), followed by interval debulking surgery (IDS) and subsequent chemotherapy as an alternative approach. The results of several retrospective analyses comparing NACT with PDS have shown a higher proportion of optimal surgery [3–6], comparable overall survival (OS) [3–6], and reduced surgical invasiveness [4,7–9] with NACT.

To further investigate the favourable outcomes associated with NACT, at least three randomised trials comparing PDS and NACT were conducted in Europe [10,11] and Japan [12]. Two previous studies—the EORTC55971 study [10], conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the CHORUS study [11], conducted by the Medical Research Council Clinical Trials Unit (MRC-CTU)—demonstrated the noninferior OS (EORTC hazard ratio [HR] 0·98 [90% confidence interval [CI] 0·84–1·13], noninferiority margin 1·25; CHORUS HR 0·87 [95% CI 0·72–1·05], noninferiority margin 1·18) and reduced invasiveness of NACT.

The Japan Clinical Oncology Group (JCOG) phase III randomised clinical trial (JCOG0602) previously clearly demonstrated the reduced invasiveness of NACT compared with PDS, in terms of the number of surgeries, operation time, blood/ascites loss and transfusions, perioperative morbidity and extent of surgery [13]. Now, the authors report the results of the study's final analysis, including the primary endpoint of OS and the major secondary endpoint of progression-free survival (PFS).

2. Patients and methods

2.1. Study design

This study was a randomised open-label phase III noninferiority trial in 34 Japanese centres or hospitals, for which the planned accrual period of three years was extended to nearly five years because of the slow accrual pace. The follow-up period after accrual completion was extended from five to six years because of the low number of events.

The trial was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review board of each participating institution before patient enrolment. This study is registered in UMIN-CTR (www.umin.ac.jp/ctr/) under identification number UMIN000000523.

2.2. Patients

This study included subjects with presumed International Federation of Gynecology and Obstetrics (FIGO, 1988) stages III or IV ovarian, tubal and peritoneal cancers diagnosed using clinical findings, including imaging studies (CT, MRI and chest radiography) and cytology of ascites, pleural effusions or tumour cyst fluids obtained by tumour centesis. Diagnostic laparoscopy or laparotomy was not performed as the previous feasibility JCOG0206 study confirmed that the target disease could be diagnosed with >90% accuracy (positive predictive value) by imaging analysis only [14]. Malignancies of different origins, e.g. breast and digestive tract, were excluded by mammography, ultrasonography, endoscopy or opaque enema whenever they were suspected from symptoms, physical examination or imaging exams. For ruling out malignancies of the digestive tract, the criteria for tumour markers were set at CA125 > 200 U/mL and CEA <20 ng/ml. Other inclusion criteria included (1) age, 20–75 years; (2) Eastern Cooperative Oncology Group (ECOG) PS, 0–3; (3) adequate bone marrow, hepatic, renal, cardiac and respiratory functions; and (4) written informed consent. The details for further inclusion and exclusion criteria are shown in the Supplementary protocol and described in previous reports [13].

2.3. Randomisation and masking

Patients were randomised to PDS or NACT arm by a minimization method with a random element [15] at the JCOG Data Center. Allocation factors for minimization were an institution, stage (III vs. IV), PS (0–1 vs. 2–3) and age (<60 vs. ≥60). Participants and investigators were not masked to treatment allocation.

2.4. Procedures

Patients assigned to PDS arm were submitted to PDS and subsequently received eight cycles of postoperative chemotherapy. IDS after the fourth cycle of chemotherapy was allowed for residual tumours >1 cm in diameter after PDS; IDS was mandatory in cases in which the uterus, adnexa or omentum was not removed by PDS, unless disease progression was noted.

Patients assigned to the NACT arm received four cycles of NACT and were subsequently submitted to IDS (unless disease progression was noted), followed by four cycles of postoperative chemotherapy.

The standard procedures for PDS in PDS arm and IDS in the NACT arm consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and maximum debulking of metastatic tumours. Systematic pelvic lymphadenectomy (PLA) and/or para-aortic lymphadenectomy (PALA) were allowed but excluded from standard procedures. All surgeries were performed under the responsibility of gynecologic oncologists certified by the Japan Society of Gynecologic Oncology. IDS during PDS treatment was performed to complete the aforementioned standard procedures. Maximum debulking of metastatic tumours and lymphadenectomies were allowed. Minimally invasive surgery, such as laparoscopic or robotic surgery, was not allowed.

Both NACT and postoperative chemotherapy comprised a combination of paclitaxel (175 mg/m^2, day 1) and carboplatin (AUC 6, day 1), namely, the TC regimen. These agents were administered every three weeks.

Detailed treatment schedules are provided in the Supplementary protocol.

Physical examination, subjective or objective symptoms and tumour marker should be evaluated every one month for two years after the protocol treatment, every two months in the third year, every three months in the fourth year and every six months thereafter. Chest X-rays and upper abdominal and pelvic imaging were performed every six months for one year, then annually along with routine examinations.

2.5. Outcomes

The study primary endpoint was OS for all randomised patients, measured from the date of registration to the date of death from any cause. The major secondary efficacy endpoint was progression-free survival (PFS), which was calculated from the date of registration to the earliest date of progression, recurrence, or death from any cause.

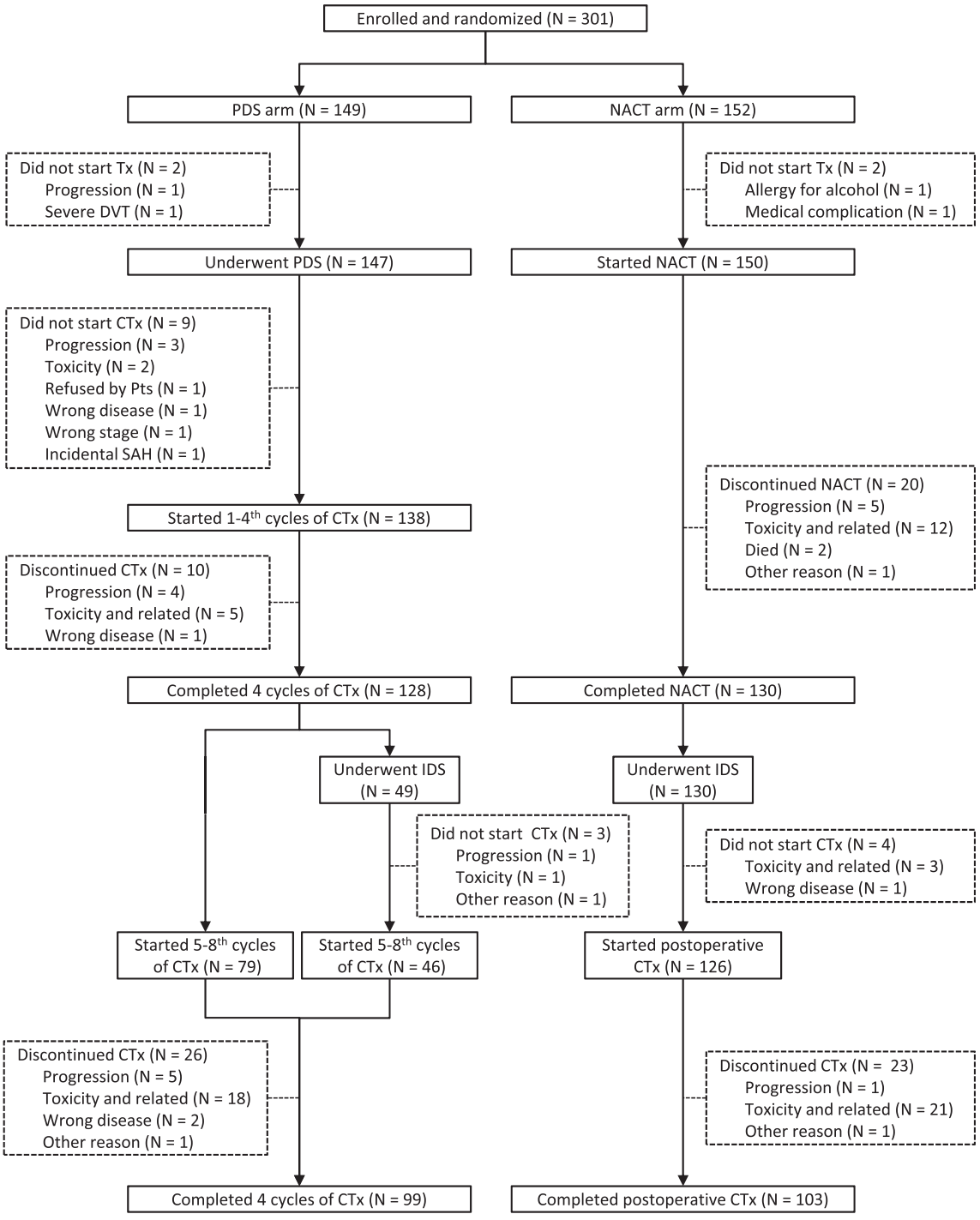

Fig. 1. **CONSORT flowchart of patient selection.** The number of enrolled and randomised patients who received treatment and were included in the analysis. Tx: treatment, CTx: chemotherapy, AE: adverse event.

2.6. Statistical analysis

After the follow-up period, the primary analysis using a Cox proportional hazard model stratified by stage, PS and age was specified to test NACT noninferiority for OS in all randomised patients. A required total event number of 276 would provide an 80% statistical power with a one-sided alpha of 0·05 to confirm the non-inferiority of NACT, with a noninferiority HR margin of 1·161. A HR of 1·161 corresponds to a 5% decrease in 3-year survival with PDS. Taking into account the accrual and follow-up periods, a sample size of 298 patients was calculated, estimating a 3-year survival of 25% with PDS and an expected 3-year survival of 30·3%

with NACT. Thus, a target sample size of 300 patients (150 patients per group) was defined. For the primary analysis of OS, the null hypothesis was "NACT is inferior to PDS (HR > 1·161)" and the alternative hypothesis was "NACT is not inferior to PDS (HR ≤ 1·161)". In the planned settings, HR of 0·953 was the boundary to reject the null hypothesis when 276 events were observed. The interim analysis was planned after enrolment of 150 patients, and additional interim analysis was planned at 2·5 years after patient assignment because of extended accrual and follow-up periods. The O'Brien–Fleming-type alpha-spending function was used to adjust multiplicity for OS.

The OS and PFS curves were calculated using the Kaplan–Meier method, and HRs and respective CIs were estimated using the Cox proportional hazard model. The total number of events observed was 226, even after extended follow-up periods. Actual statistical power became 73%. Adverse events and surgical invasiveness had already been shown in a previous report [13]. All analyses were conducted in the statistical program SAS Release 9·4 (SAS Institute, Cary, NC).

3. Results

From November 2006 to October 2011, 301 patients were enrolled in the study. All patients were randomly assigned to PDS or NACT (Fig. 1). A total of 149 patients were assigned to the PDS arm; 147 of these patients underwent PDS, 49 of which underwent IDS. A total of 152 patients were assigned to the NACT arm, 150 of whom received NACT and 130 of them underwent IDS. All randomised 301 patients were included in the primary analysis. Patients' characteristics and the number of chemotherapy cycles received are listed in Table 1. Over 30% of patients had stage IV disease, and approximately 13% had PS 2/3 in each treatment arm. All adjustment factors were equally distributed. The median number of chemotherapy cycles was eight for both arms.

Histological diagnosis, median operation time, and frequency of surgical procedures are listed in Table 2. Serous histology was observed in nearly 80% of patients in each arm, and chemo-resistant histology (clear and mucinous adenocarcinoma) was observed in 9·5% and 4·6% of patients in the PDS and NACT arms, respectively. Both complete and optimal surgeries were more frequently achieved with IDS in the NACT arm than with PDS or PDS ± IDS in the PDS arm (63·8% vs. 11·6% or 30·6%, and 82·3% vs. 37·4% or 62·6%, respectively).

The median OS values for all patients randomised were 49·0 and 44·3 months (M) in the PDS and NACT arms, respectively (Fig. 2A). For the primary analysis, the significance level of 0·046 was used for adjusting multiplicity owing to interim analyses. The noninferiority HR for OS of NACT compared with PDS was 1·052 (90·8% CI 0·835–1·326; P = 0·24). The proportional hazard assumption was checked using a log–log plot, and no serious problem was observed.

The median PFS values were 15·1 and 16·4 M in the PDS and NACT arms, respectively (Fig. 2B), with a HR of 0·96 (95% CI 0·75–1·23) for noninferiority of NACT.

Fig. 3 shows the OS according to treatment arm and debulking results. The median OS values for patients with 0, <1, and ≥1 cm residual tumours were following; not estimable, 54·9 M, and 43·0 M in the PDS arm and 67·0, 34·0, and 32·0 M in the NACT arm, respectively. Adverse events and surgical invasiveness had already been shown in a previous report [13].

To identify subgroups of patients or institutions with better OS associated with either of the study arms, forest plots were shown according to different prognostic factors (Fig. 4). Considering patients' characteristics, the HR of NACT was considerably lower in subgroups with poor PS (2 or 3), low albumin (≤2·5 g/dL), and high CA125 (>2000 U/mL), whereas it was considerably higher in subgroups with chemo-resistant histology (pathologically clear and mucinous). Concerning

Table 1
Baseline patient characteristics (for all patients enrolled).

Treatment arm	PDS (N = 149)	NACT (N = 152)
Median age (range)	59 (30–75)	60·5 (36–75)
Age		
<60	75 (50·3%)	72 (47·4%)
≥60	74 (49·7%)	80 (52·6%)
PS		
0–1	130 (87·2%)	131 (86·2%)
2–3	19 (12·8%)	21 (13·8%)
Stage		
III	100 (67·1%)	105 (69·1%)
IV	49 (32·9%)	47 (30·9%)
Primary tumour[a]		
Ovary	131 (87·9%)	125 (82·2%)
Fallopian tube	1 (0·7%)	1 (0·7%)
Peritoneum	23 (15·4%)	34 (22·4%)
Measurable lesions		
present	140 (94·0%)	142 (93·4%)
absent	9 (6·0%)	10 (6·6%)
CA125(U/mL)		
≤500	24 (16·1%)	29 (19·1%)
≤1000	25 (16·8%)	34 (22·4%)
≤2000	26 (17·4%)	24 (15·8%)
>2000	74 (49·7%)	65 (42·8%)
Size of upper abdominal tumour		
≤2 cm	32 (21·5%)	42 (27·6%)
≤5 cm	42 (28·2%)	51 (33·6%)
≤10 cm	40 (26·8%)	35 (23·0%)
>10 cm	35 (23·5%)	24 (15·8%)
Chemotherapy cycles		
Median (25%–75%)	8 (6–8)	8 (7–8)
Average ± SD	6·7 ± 2·5	6·8 ± 2·2

PDS, primary debulking surgery; NACT, neoadjuvant chemotherapy; PS; performance status; SD, standard deviation.
[a] Selection of multiple sites was allowed if it was difficult to specify one primary site.

Table 2
Histology diagnosed from surgical specimens and surgery-related factors.

Treatment arm	PDS (N = 149)			NACT (N = 152)
Surgery	PDS (N = 147)	IDS (N = 49)	PDS ± IDS (N = 147)	IDS (N = 130)
Histology				
Serous	115 (78·2%)			102 (78·5%)
Endometrioid	6 (4·1%)			4 (3·1%)
Mucinous	2 (1·4%)			2 (1·5%)
Clear	12 (8·2%)			4 (3·1%)
Mixed	4 (2·7%)			1 (0·8%)
Others	8 (5·4%)			17 (13·1%)
Median operation time (min)	240	270	347	302
Surgical outcome				
RT = 0	17 (11·6%)	28 (57·1%)	45 (30·6%)	83 (63·8%)
RT < 1 cm	38 (25·9%)	9 (18·4%)	47 (32·0%)	24 (18·5%)
RT ≥ 1 cm	92 (62·6%)	12 (24·5%)	55 (37·4%)	23 (17·7%)
Surgical procedures				
Pelvic lymphadenectomy	40 (27·2%)	19 (38·8%)	59 (40·1%)	94 (72·3%)
Para-aortic lymphadenectomy	17 (11·6%)	12 (24·5%)	29 (19·7%)	64 (49·2%)
Abdominal organ resection	40 (27·2%)	17 (34·7%)	56 (38·1%)	36 (27·7%)

PDS, primary debulking surgery; NACT, neoadjuvant chemotherapy; IDS, interval debulking surgery; RT, residual tumour.

institution features, the HR of NACT was lower in the subgroup with low study activity (<20 total patient accruals) and higher in the subgroup with high study activity (≥20 total patient accruals). A similar HR was found for subgroups with high (>60%) and low (<60%) proportions of optimal debulking in PDS (HR = 1·12 vs. 1·05).

4. Discussion

Compared with PDS, a survival noninferiority of NACT was not confirmed in this study. This disagrees with previous phase III randomised studies (EORTC55971 [10] and CHORUS [11]), which showed noninferior OS of NACT compared with PDS. The results of these two studies and the present one are summarised in Table 3. The possible reasons for the disparate results are different study designs, treatment protocols and surgical outcomes along with the lower statistical power in our study.

Compared with previous studies, in this study, IDS was more frequently performed in PDS arm (33% vs. 17% and not described [probably less frequent] in EORTC [10] and CHORUS[11], respectively). One reason for the higher incidence of IDS was lower rates of complete and optimal debulking at PDS compared with previous studies. Another reason was a wide indication of IDS in our study; it allowed for patients with suboptimal PDS and mandatory in cases the uterus, adnexa, or omentum was not removed by PDS. Although the treatment efficacy of IDS following suboptimal PDS was demonstrated by another EORTC phase III trial [16], a randomised trial conducted after the EORTC study by Gynecologic Oncology Group did not corroborate this efficacy benefit [17]. Owing to these results, EORTC 55971 institutions may hesitate to perform IDS, although it is recommended in their treatment protocol following nonoptimal PDS. In the CHORUS trial, institutions had to specify patients before randomisation to perform IDS. The protocol setting in CHORUS might preclude the IDS. However, a Cochran systematic review with meta-analysis concluded that IDS yields benefit only for women with a primary surgery not performed by gynecologic oncologists or less extensive [18]. This means that patients with insufficient PDS may benefit from IDS. Considering the highly suboptimal rate of PDS in the present study, more patients in the PDS arm may benefit from IDS. A higher percentage of IDS might have improved OS associated with PDS in the present study. Conversely, 20 patients (13%) did not undergo IDS in the NACT arm; this may have worsened the outcome of NACT; however, the frequency in our study was not much higher than in previous studies (11% in EORTC and 20% in CHORUS).

Although NACT had an apparent advantage in stage IV patients [19] in the pooled analysis of the two previous studies, this was not confirmed in this study. Although the HR for NACT was similar in both analyses for stage III patients (1·04 and 1·04, respectively), it was much lower in the pooled analysis than in the present study for stage IV patients (0·76 [median OS, 21·2 and 23·2 M in PDS and NACT, respectively] vs. 1·15 [median OS, 45·7 and 46·0 M in PDS and NACT, respectively]). The outcomes of patients with stage IV ovarian cancer receiving PDS were poorer in the two previous studies, which may be due to two disparate reasons. On the one hand, there was a higher frequency of postoperative deaths with PDS in those studies (2·5% in EORTC and 6% in CHORUS) compared to ours (0·7%), potentially worsening the PDS outcomes. The lower incidence may be related to less aggressive PDS in

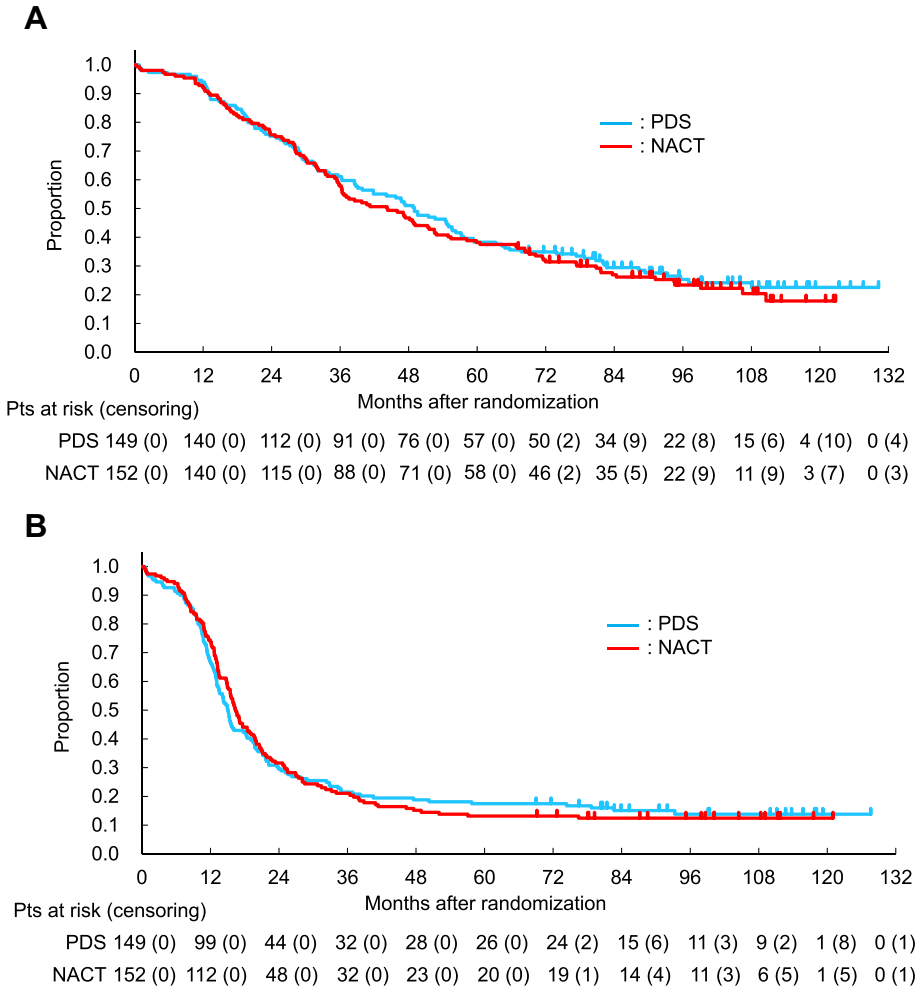

Fig. 2. **Prognosis of patients enrolled. Overall survival.** (A) and progression-free survival (B) of patients who were enrolled in the study. HR for death with NACT compared with PDS was 1·052 (90·8% CI, 0·835–1·326; P = 0·24 for noninferiority calculated using the Cox proportional hazard model stratified by FIGO stage, PS and age) (A). HR for progression with NACT compared with PDS was 0·96 (95% CI, 0·75–1·23 calculated by the Cox proportional hazard model stratified by theFIGO stage, PS and age) (B).

the present study. On the other hand, there may be some reluctance by clinicians to perform aggressive maximum debulking surgery, especially in stage IV patients. In the present study, the opportunity to perform IDS as second surgery in the PDS arm may have given a safe and rather aggressive treatment option for stage IV patients in that treatment arm. The absence of an advantage of NACT in stage IV patients in the present study may also explain why our results did not match those from previous studies.

Regarding chemotherapy cycle numbers in NACT, four cycles used in this study were larger than three cycles used in the previous two studies. NACT may more frequently induce chemo-resistance because of the larger tumour volume at the initiation of chemotherapy [20–22]. Possibly, our four-cycle NACT regimen may have induced a higher frequency of chemo-resistance because post-progression survival in NACT was 6 months shorter than that in PDS in this study; however, the survivals were almost the same in the previous two studies.

As for the age, our study limited the age to ≤75 years old in contrast to previous studies, those made no age limitation. Advanced age is known to be an important prognostic factor for ovarian cancer [23], and NACT is proposed as an effective way of managing elderly patients [24]. The age limitation in the present study may contribute to better OS in both arms and worse NACT efficacy compared with previous studies.

The present study showed that institutions with high surgical activity (proportion of optimal surgery in PDS > 60% [mean; 74%]) achieved better OS than those with low surgical activity (mean; 24%) in both PDS and NACT (56·9 M and 49·5 M vs. 46·8 M and 42·4 M, Supplementary Table 1). As a result, a similar HR for NACT (HR = 1·12 vs. HR = 1·05) was observed between institutions with high and low surgical activity (Fig. 4), because institutions with high and low surgical

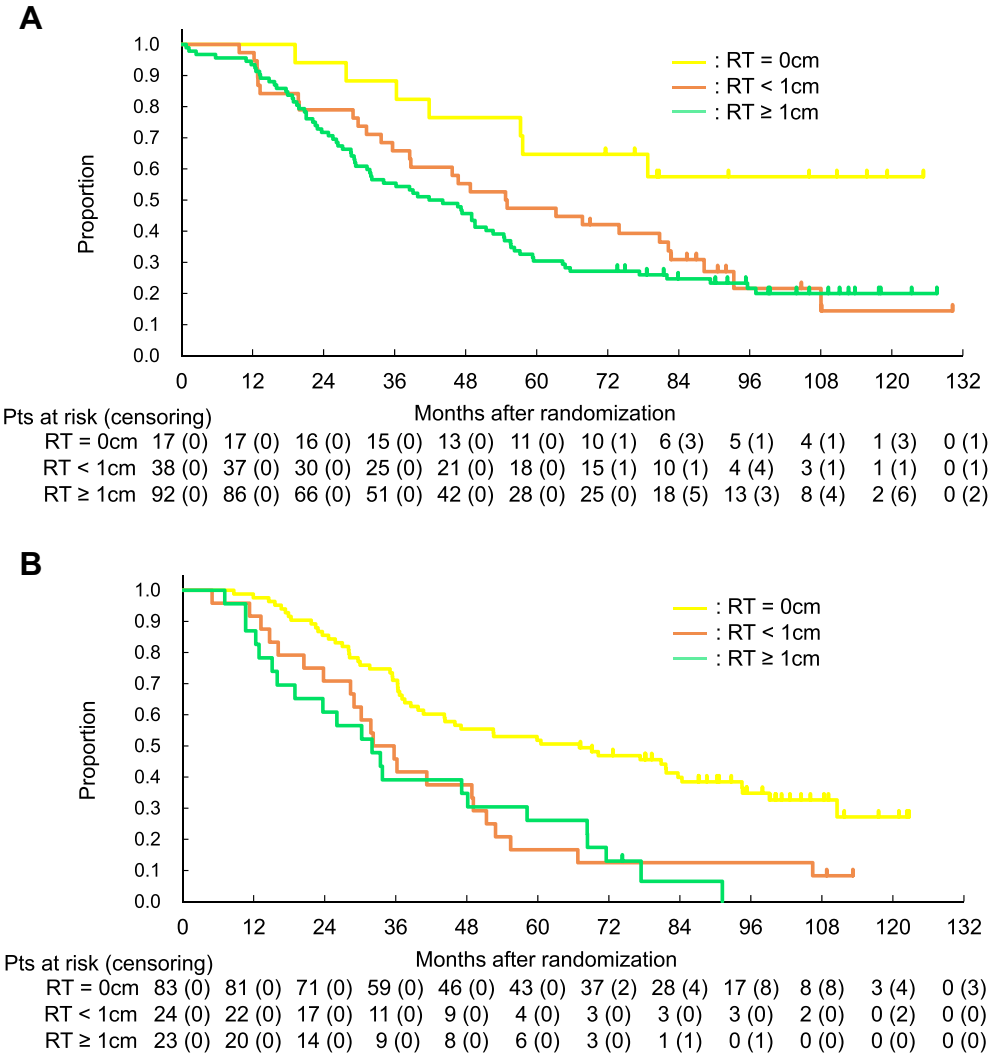

Fig. 3. **Overall survival, according to the residual tumour size at debulking surgery.** Overall survival for patients treated with PDS (A) and NACT (B) according to residual tumour size at debulking surgery. In PDS, 49 patients who underwent both PDS and IDS were classified according to the residual tumour size at PDS without considering IDS results. In NACT, 20 patients who did not undergo IDS were excluded from this analysis.

activity in PDS had similar high and low surgical activity also in IDS in NACT (proportion of complete surgery; 80% vs. 59%). Although our data suggest that surgical activity is not so related to superiority or inferiority of NACT compared with PDS, we must expect the results of new phase III studies comparing PDS and NACT among institutions achieving complete resection in ≥50% PDS —TRUST and SUNNY (ClinicalTrials.gov NCT02859038 and NCT02828618) —conducted by Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) and the Shanghai Gynecologic Oncology Group (SGOG).

Concerning the other subset analyses, patients with poor PS (2 or 3), low albumin (≤2·5 g/dL), and high CA125 (>2000 U/mL) showed favourable treatment outcomes with NACT in this study's subgroup analyses. These findings are in line with previous studies showing these features as unfavourable prognostic factors or predictors for suboptimal debulking with PDS [23,25]. High CA125 (>2000 U/mL) indicates serous histology or chemo-sensitivity. In previous studies, a higher frequency of PS 2 (CHORUS) or undifferentiated histology (CHORUS and EORTC) may have improved treatment results with NACT. In this study, although the number of patients was small, PDS was associated with relatively better treatment outcomes in patients with clear-cell or mucinous histology. These results suggest that there is diversity in the efficacy of PDS and NACT among various subgroups of advanced ovarian cancer.

On the basis of the results from the CHORUS and EORTC trials [10,11], our preceding study concerning treatment invasiveness [13], and another phase III trial [26], the American Society of Clinical Oncology (ASCO) [27] and the Society of Gynecologic Oncology (SGO) [28] copublished guidelines for the treatment of

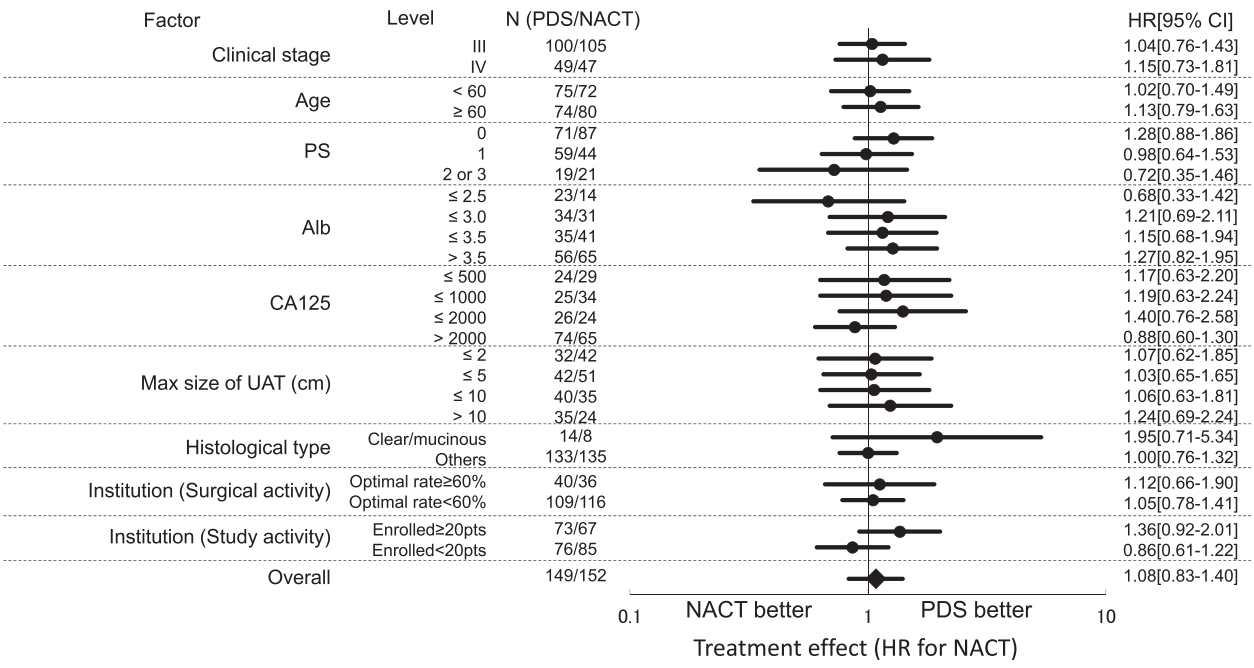

Fig. 4. **Treatment effect for NACT on overall survival in subgroups.** Treatment effect with NACT compared with PDS in several subgroups. UAT: upper abdominal tumour.

advanced ovarian cancer in 2016. The guidelines generally recommend NACT for all patients, except for those with optimally resectable tumours and a general condition suitable for surgery. Concurrently (or previously), NACT had become more widely accepted as one of the standard treatment options for such advanced ovarian cancer patients [29,30]. In fact, the results from three randomised studies, including ours, suggest that NACT is a safer treatment for ovarian cancer. However, regarding the efficacy results, our results demonstrated that NACT may not always be a good substitute for PDS in advanced ovarian tumours, suggesting that patients who are candidates for NACT should be selected on the basis of resectability, general condition, nutrition and supposed chemo-sensitivity. This study's results were generally in line with the guidelines.

This study has some limitations. First, the sample size in our study was rather small than that in previous studies. Further, the reduction of statistical power to 73% owing to fewer events than expected was also a shortcoming of our study. However, even if the number of events was 276 as planned, noninferiority could not

Table 3
Comparison of treatment results of three phase III studies.

Study	EORTC		CHORUS		JCOG	
Treatment arm	PDS (N = 336)	NACT (N = 334)	PDS (N = 276)	NACT (N = 274)	PDS (N = 149)	NACT (N = 152)
Surgery	PDS (N = 310)	IDS (N = 322)	PDS (N = 251)	IDS (N = 217)	PDS (N = 147)	IDS (N = 130)
Surgical outcome and procedures						
Operation time	165	180	120	120	240	302
RT = 0	61 (19%)	151 (51%)	39 (17%)	79 (39%)	17 (12%)	83 (64%)
RT < 1 cm	70 (22%)	87 (30%)	57 (24%)	68 (34%)	38 (26%)	24 (18%)
RT ≥ 1 cm	167 (53%)	52 (18%)	137 (59%)	54 (27%)	92 (63%)	23 (18%)
Survival outcomes						
PFS (Months)	12	12	10·7	12·0	15·1	16·4
OS (Months)	29	30	22·6	24·1	49·0	44·3
Statistical factors						
HR for NACT in OS	0·98		0·87		1·05	
Confidence Interval (CI)	90% CI 0·84–1·13		95% CI 0·72–1·05		90·8% CI 0·83–1·33	
Noninferiority margin	1·25		1·18		1·161	
P value for noninferiority	0·01		NA		0·24	

PDS, primary debulking surgery; NACT, neoadjuvant chemotherapy; IDS, interval debulking surgery; RT, residual tumour; PFS, progression-free survival; OS, overall survival; PLA, pelvic lymphadenectomy; PALA, para-aortic lymphadenectomy; HR, hazard ratio; NA, not available.

be confirmed because observed HR of 1·052 exceeded the boundary of 0·953 in planned settings. Second, although the HR for NACT was rather higher in subgroups with clear and mucinous histology, the study protocol did not require histological confirmation by surgery at the start of treatment in NACT arm. Consequently, it may be inappropriate to discuss the histological diagnosis in NACT in this study.

In conclusion, the OS noninferiority of NACT was not confirmed. The data suggest that NACT may not always be a substitute for PDS. Our study had a smaller sample size; therefore, we cannot deny the noninferiority evidence of NACT confirmed by the previous two studies. There seems to be diversity in the efficacy of PDS or NACT among subgroups of advanced ovarian cancer.

Contribution of authors

TO[1] and HY[19] were involved in the conception, design and management of the study. TO[1] and HY[19] were also involved in patient recruitment, data collection, data analysis, interpretation and manuscript writing. TS[2], TS[4], TK[5], TN[6], KT[7], AO[8], KU[9], HK[10], KK[11], HY[12], MT[13], HK[14], YW[15], KY[16], NY[17], TK[18] were involved in patient recruitment, data collection and contributed to manuscript writing. TM[3] was involved in data collection, analysis, interpretation and contributed to manuscript writing. GO[3] was responsible for statistical analysis and interpretation, and contributed to manuscript writing. All authors reviewed the final version of the manuscript.

Conflict of interest statement

TO[1] received grant and personal fee from Chugai, grants from Kaken, Taiho, Daiichi-Sankyo, Mochida, and Meiji Yasuda Health Development Foundation, and personal fees from AstraZeneca and Ono outside the submitted work. TS[2] reported personal fees from Mochida, Nippon Kayaku, Chugai, Daiichi-Sankyo, Kyowa Kirin, AstraZeneca, Kaken, Eisai, Tsumura, Beyer, and Aska outside the submitted work. TS[4] reported grants and personal fees from Chugai and Nippon Kayaku, and grants from Taiho and Yakult outside the submitted work. KT[7] reported other financial activities from AstraZeneca, Daiichi Sankyo, Chugai, and Eisai outside the submitted work. AO[8] reported other financial activities from Taiho, Meiji, Fuji, Nippon Shinyaku, Novartis, Mochida, Chugai, Tsumura, Pfizer, Kissei, Shionogi, Daiichi Sankyo, Kaken, GenoDive, CMIC, and Shinnihonseiyaku, and personal fee from AstraZeneca outside the submitted work. KU[9] received grants and personal fees from AstraZeneca, MSD, Chugai, Kaken, Takeda, Nippon Kayaku, Mochida, and Tsumura, and grants from Abbvie, Ono, and Eisai, and personal fees from Taiho, Yakult, Kyowa Kirin, Bayer, and Aska outside the submitted work. HY[12] received grants from MSD and Zeria, and personal fees from Kaken, Ono, AstraZeneca and Chugai, and Pfizer outside the submitted work. TK[18] reported a personal fee from BrightPath Biotherapeutics outside the submitted work. HY[19] reported personal fees from Ono, Taiho, MSD, and GSK outside the submitted work. GO[3], TK[5], TM[3], TN[6], HK[10], KK[11], MT[13], HK[14], YW[15], KY[16], NY[17] reported no competing interests.

Acknowledgments

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Funding source

The study was supported by Health Sciences Research Grants for the Third-Term Comprehensive Control Research for Cancer (H16-035), Health Sciences Research Grants for Clinical Cancer Research (H19–028, H22-020), Grants-in Aid for Cancer Research (17S-1, 17S-5, 18-06, 20S-1, 20S-6) from the Ministry of Health, Labour and Welfare, Japan, and the National Cancer Center Research and Development Funds (23-A-16, 23-A-17, 26-A-4, and 29-A-3).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.02.020.

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