



# Feasibility of initial treatment in elderly patients with ovarian cancer in Japan: a retrospective study

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## Abstract

**Purpose** The purpose of this study was to evaluate the real world situation and clarify the problem in initial treatment for elderly patients with ovarian cancer in Japan.

**Methods** We used the ovarian cancer database, containing all patients diagnosed and treated with International Federation of Gynecology and Obstetrics Stage I–IV ovarian cancer at the National Cancer Center Hospital in Japan from June 2008 to April 2013. Patients were stratified into two groups based on age: an elderly group, aged 70 years or older, and a younger group, aged below 70 years. We retrospectively assessed the rate of receiving standard therapy, and the feasibility and safety of chemotherapy compared with younger patients.

**Results** In total, 244 patients (elderly group, 36 patients; younger group, 208 patients) were analyzed. A significantly lower proportion of elderly patients than younger patients received standard therapy (15.7% vs. 32.5%,  $p=0.026$ ). Even for the elderly group, 95% patients underwent surgery in our institution. Conversely the rate of patients receiving nonstandard chemotherapy in the elderly group was significantly higher than in the younger group (30.5% vs. 9.6%,  $p=0.01$ ).

**Conclusions** This study clarified the type of treatment being performed in the field, and the proportion of elderly ovarian cancer patients receiving standard therapy compared with younger patients in Japan. In addition, the actual situation of elderly patients in Japan might be different from that in Western countries. We need to evaluate the appropriate treatment for elderly patients in Japan.

**Keywords** Elderly patients · Ovarian cancer · Standard therapy · Relative dose intensity · Feasibility

## Background

Ovarian, fallopian tube, or peritoneal cancer (ovarian cancer) are the tenth most common cancer among women in Japan, who have a high life expectancy, with the risk of ovarian cancer increasing proportionally with age. In general, there is a multiphysiological system decline, so called frailty, which increases with age, with a decreased tolerance to stresses. However, there are individual differences in the frailty of the elderly that are influenced by various factors. The frailty or vulnerability of elderly cancer patients needs to be evaluated and managed properly in cancer therapy. In Japan especially, the population is aging at the fastest rate in the world. Therefore, it was necessary to consider the current state of treatment for elderly cancer patients, including for ovarian cancer.

No upper age limit is set in most clinical trials for ovarian cancer [1–3], and, in subset analysis, a number of clinical

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trials show that the benefit in progression survival or overall survival of standard chemotherapy is applicable to elderly patients. In our previous report, elderly patients with good performance status (PS) were able to tolerate dose dense paclitaxel (PTX) and carboplatin (CBDCA) therapy (ddTC therapy), with 86.4% completing six courses, similar to the younger aged control group [4]. These results suggest that ‘fit’ elderly patients, who were defined as ‘not vulnerable’ in usual care or who could participate in a clinical trial, could receive standard therapy and might benefit from this. However, the appropriate treatment for vulnerable or frail patients is still not clear.

In Western countries, there have been several reports and prospective trials conducted to determine the current treatment level, and assess its appropriateness for elderly ovarian cancer patients [5–8]. It is possible that patients from some different backgrounds, such as Caucasian, compared with Asian people, including Japanese, might have different feasibility for treatment, or different rates of survival, because of physiological, clinicopathological, medical system, or socioeconomic differences [9]. It is necessary to clarify the problem in elderly cancer patients in own country to plan for aging society. However, there are, to date, few reports investigating cancer treatment in elderly patients in Japan.

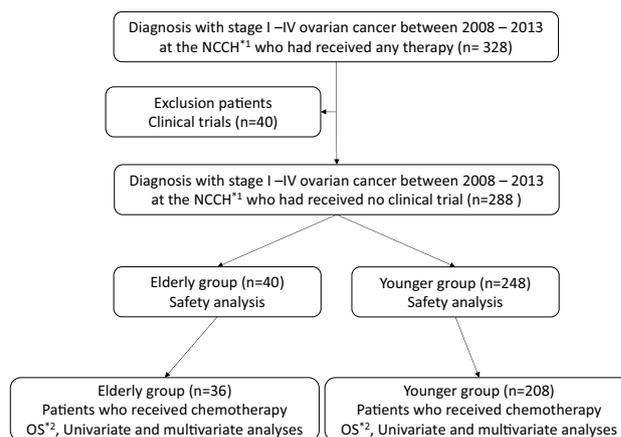
The purpose of this study was to evaluate the real world situation and clarify the problem in initial treatment for elderly patients with ovarian cancer in Japan.

## Patients and methods

### Patients

This study is a single center, retrospective study. We performed this study with approval from the National Cancer Center Institutional Review Board (No. 2013–263) in accordance with guidelines on medical and epidemiological research in an epidemiologic study. After obtaining institutional review board approval, the ovarian cancer database containing all patients treated at the National Cancer Center Hospital in Japan from June 2008 to April 2013 was used to identify all the patients diagnosed with International Federation of Gynecology and Obstetrics (FIGO) Stage I to IV ovarian, fallopian tube, or primary peritoneal cancer (ovarian cancer). We excluded patients who were assigned to clinical trials (Fig. 1).

Patients were stratified into two groups based on age: elderly group, patients aged 70 years or older, and younger group, patients aged below 70 years, according to the definitions used in Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens (GINECO) or Multicentre Italian Trial in Ovarian cancer (MITO) trials [7, 10, 11].



**Fig. 1** Patient selection flow diagram. <sup>1</sup>NCCH National Cancer Center Hospital, <sup>2</sup>OS overall survival

**Table 1** Definition of standard therapy

FIGO stage	Histology type	Grade	Surgery	Chemotherapy
IA/IB	Except Clear	1	PDS	No
	Clear	–	PDS	Conventional TC
	Except Clear	2,3	PDS	Conventional TC
IC	Any	Any	PDS	Conventional TC
II	Any	Any	PDS	Dose-dense TC
III	Any	Any	PDS/IDS	Dose-dense TC
IV	Any	Any	PDS/IDS	Dose-dense TC

FIGO International Federation of Gynecology and Obstetrics (2008), PDS primary debulking surgery, IDS interval debulking surgery, TC combination of carboplatin and paclitaxel therapy

### Definition of standard therapy

We defined the “standard therapy” group as patients who underwent surgery and / or chemotherapy as recommended in our institute based on the stage, histology and grade of cancer (Table 1). In this study, we defined the “nonstandard therapy” group as patients who did not receive “standard therapy”. This occurred for a wide range of reasons.

Patients who were assessed to be suitable, received an abdominal total hysterectomy, bilateral salpingo-oophorectomy and omentectomy performed by a gynecologic oncologist. All primary debulking surgery (PDS) or interval debulking surgery (IDS) were performed with care to achieve complete resection, including at the metastatic site. Pelvic lymph-node or para-aortic lymph-node resection was performed in patients with suspicious nodes. If lymph-node metastasis was confirmed using a rapid frozen section procedure, we performed pelvic and para-aortic lymph-node resection. Peritoneal stripping

was performed for patients with peritoneal metastasis, if gynecologist defined to be achieved optimal resection. DdTC therapy consisted of PTX (80 mg/m<sup>2</sup> on days 1, 8, and 15) and CBDCA (AUC 6 mg/mL per min on day 1) in a 21-day cycle. Conventional TC therapy consisted of PTX (175 mg/m<sup>2</sup> on day 1) and CBDCA (AUC 6 mg/mL per min on day 1) in a 21-day cycle. Weekly TC therapy consisted of PTX (80 mg/m<sup>2</sup> on days 1, 8, 15) and CBDCA (AUC 2 mg/mL per min on days 1, 8, 15) in a 21-day cycle. DC therapy consisted of docetaxel (70 mg/m<sup>2</sup> on day 1) and CBDCA (AUC 5 mg/mL per min on day 1) in a 21-day cycle. According to the protocol, all patients needed to have healthy organ and bone marrow function to receive subsequent cycles of chemotherapy [1, 12]. Each treatment was repeated for a total of six cycles.

### Data collection

Detailed data were collected from patient records. Clinical characteristics included: age; diagnosis; FIGO stage; histological type; grade; PS; relative dose intensity (RDI) for each regimen; adverse events; rate and reasons for the discontinuation of therapy; proportion of patients who underwent blood transfusion; and overall prognosis. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0 [13]. Surgical information regarding residual tumor volume was obtained, and optimal surgery was defined as no residual tumor or residual tumor of less than 1 cm in diameter.

RDI was calculated as the ratio of actual total dose intensity to planned total dose intensity.

$$\text{RDI} = (\text{actual total dose [mg]}/\text{actual duration of therapy [week]})/(\text{planned total dose [mg]}/\text{planned duration of therapy [weeks]}).$$

### Statistical analysis

We compared RDI, incidence of adverse events, and rate of chemotherapy discontinuation between the elderly group and the younger group using the chi-square test. The Kaplan–Meier method was used to estimate overall survival (OS), which was calculated as the time from the date when any therapy was started to death of the patient. Patients that remained alive were censored on the date of last follow-up. Univariate and multivariate analyses were performed in patients with Stage II–IV cancer. Variables considered in the analyses included age, Eastern Cooperative Oncology Group PS (0–1, 2–4), FIGO stage (II, III–IV), histology (serous/endometrioid, clear/mucinous/adenocarcinoma/other), residual disease (optimal, suboptimal), and RDI for each regimen. In multivariate analyses, we included variables with a  $p < 0.05$  in the univariate analyses. All statistical tests were two-sided, and  $p < 0.05$

were considered statistically significant. All statistical analyses were performed with EZR, version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics [14].

## Results

### Patient characteristics

A total of 244 patients (elderly group, 36 patients; younger group, 208 patients) were analyzed. There was no patient who did not receive at least one of surgery or chemotherapy. The median age in the elderly group was 74 years (range 70–85), compared with 54 years (range 16–69) in the younger group. Most patients had PS of 0 or 1 elderly group 91.6%; younger group, 92.7%,  $p = 0.94$ . Most patients underwent primary or interval debulking surgery elderly group 94.4%; younger group 95.1%, however, most elderly patients received IDS 44.4%. For histological type, there were no significant differences between the two groups (Table 2).

### Rate of standard therapy

A significant difference was observed between the proportion of elderly and younger patients who received standard therapy ( $p = 0.026$ ). All patients with stage I cancer received standard therapy. Those in the elderly group with Stage II–IV cancers received nonstandard therapy more frequently than those in the younger group (Table 3). There was no significant difference between the two groups in the proportion of patients who underwent surgery (Table 4). Even for the elderly group, 95% patients underwent surgery in our institution. Conversely the rate of patients receiving nonstandard chemotherapy in the elderly group was significantly higher than in the younger group 30.6% vs. 9.6%,  $p = 0.01$ . The most frequent reason for this was regimen change; in particular, patients in the elderly group more frequently received the weekly TC (Table 4). The reason for selective the less toxic regimen was partially overlapping each other.

### Relative dose intensity (RDI)

There were no significant differences in RDI between the elderly group and the younger group (elderly group, 73.7% vs. younger group, 79.7%;  $p = 0.065$ ).

**Table 2** Patient characteristics

	Elderly group (n = 36)	Younger group (n = 208)	p value
Age (years)	74 (70–85)	54 (16–69)	
FIGO stage			0.008
I	3 (8.3)	64 (30.7)	
II	7 (19.4)	19(9.1)	
III	20 (55.5)	84 (40.3)	
IV	6 (16.6)	41 (19.7)	
ECOG performance status			0.004
0	19 (52.7)	152 (73.0)	
1	14 (38.8)	41 (19.7)	
2	2 (5.5)	12 (5.7)	
3–4	1 (2.7)	3 (1.4)	
Surgery			0.077
Primary debulking	18 (50.0)	142 (68.2)	
Interval debulking	16 (44.4)	56 (26.9)	
None	2 (5.5)	10 (4.8)	
Residual disease			0.468
Complete	10 (27.7)	52 (25.0)	
Optimal	19 (52.7)	128 (61.5)	
Suboptimal	7 (19.4)	28 (13.4)	
Histological subtype			0.302
Serous	18 (50.0)	103 (49.5)	
Endometrioid	5 (13.8)	34 (16.3)	
Mucinous	2 (5.5)	14 (6.7)	
Clear cell	4 (11.1)	40 (19.2)	
Other	7 (19.4)	17 (8.1)	

Data are n (%) or medians (range)

FIGO International Federation of Gynecology and Obstetrics, ECOG Eastern Cooperative Oncology Group

**Table 3** Rate of standard therapy for patients with cancers of each stage

FIGO stage	Elderly group (n = 36)		Younger group (n = 208)		p value
	Standard	Nonstandard	Standard	Nonstandard	
IA/IB	1 (100)	0	23 (92.0)	2 (8.0)	N.S.
IC	2 (100)	0	34 (87.1)	5 (12.8)	N.S.
II	1 (14.2)	6 (85.7)	9 (47.3)	10 (52.6)	N.S.
III	17 (47.2)	3 (15.0)	75 (89.2)	9 (10.7)	0.015
IV	2 (33.3)	4 (66.6)	28 (68.2)	13 (31.7)	N.S.
All stage	23 (57.5)	13 (32.5)	169 (68.1)	39 (15.7)	0.026

Data are n. FIGO International Federation of Gynecology and Obstetrics

“Standard” means standard therapy see Table 1. “nonstandard” means without standard therapy

**Table 4** Reasons for nonstandard therapy

	Elderly group (%)	Younger group (%)
The number of all patients	36	208
Surgery	2 (5.6)	10 (4.8)
Refusal	1	1
No indication	1	8
Unknown	0	1
Chemotherapy*	11 (30.6)**	20 (9.6)**
Refusal	0	2
No indication	0	1
Weekly TC	5	3
Old age	5	0
Comorbidity	1	1
Poor PS (3 or greater)	1	2
TC	2	10
Too far to come hospital	1	2
Patients request	1	1
Unknown	0	7
DC	3	4
Weak alcohol	2	3
Refusal of peripheral neuropathy	1	1

\*There were no patients with stage I cancer. All were stage II–IV cancers

\*\*p < 0.01

## Toxicity

Hematological and nonhematological toxicity in the two groups were similar (Table 5). There were no significant differences in the proportion of patients with anemia of Grade 3 or higher (elderly group, 19.4% vs. younger group, 14.9%;  $p = 0.463$ ), neutropenia of grade 3 or higher (elderly group, 58.3% vs. younger group, 42.7%;  $p = 0.103$ ), and thrombocytopenia of grade 3 or higher (elderly group, 13.8% vs. younger group, 21.1%;  $p = 0.375$ ). Prophylactic granulocyte-colony stimulating factor was not used in either group. Nonhematological toxicity was mild, other than the significantly higher rate of severe peripheral neuropathy (Grade 2 or higher) observed in the elderly group (elderly group, 50% vs. younger group, 25%;  $p = 0.004$ ). The rates of discontinuation of chemotherapy (elderly group 5.5% vs. younger group 6.7%) and emergency hospital admission (elderly group 5.5% vs. younger group, 3.3%) were low in both groups (Table 5). No treatment-related deaths were observed during chemotherapy.

## Overall survival

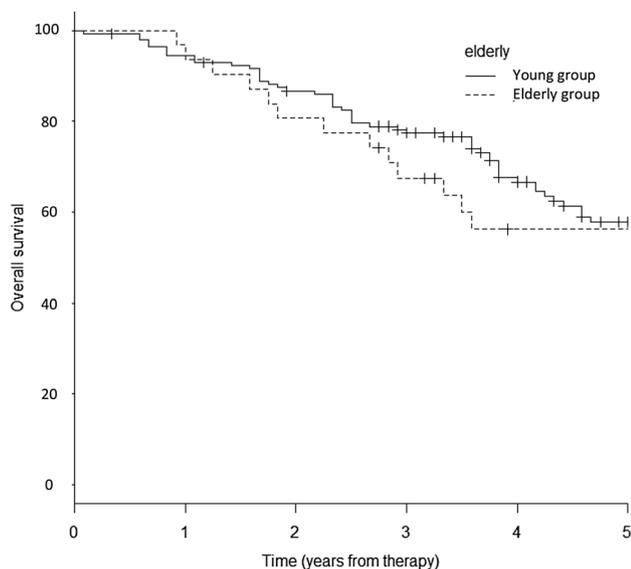
Median follow-up of the surviving patients with stage II–IV cancer was 46 months (range 1–106). There were no

**Table 5** Treatment-related toxicity and supportive care provided during chemotherapy

	Elderly group ( <i>n</i> = 36)	Younger group ( <i>n</i> = 205)	<i>p</i> value
Anemia (grade 3 or higher)	7 (19.4)	31 (15.1)	0.468
Neutropenia (grade 3 or higher)	21 (58.3)	89 (43.4)	0.106
Thrombocytopenia (grade 3 or higher)	5 (13.8)	44 (21.6)	0.373
Peripheral neuropathy (grade 2 or higher)	18 (50)	52 (25.4)	0.004
Febrile neutropenia	5 (13.8)	11 (5.4)	0.071
Nausea (grade 2 or higher)	4 (11.1)	35 (15.1)	0.468
Blood transfusion	7 (19.4)	31 (15.1)	0.468
Emergency hospital admission	2 (5.5)	7 (3.4)	NE
Chemotherapy induced infection	2	0	
Caused by ileus	0	7	
Discontinuation of chemotherapy	2 (5.5)	14 (6.7)	NE
Chemotherapy toxicity	1	3	
Caused by disease progression	0	2	
Patients refusal	0	2	
Other reason	1	7	

Data are *n* (%)

NE not evaluated

**Fig. 2** Kaplan–Meier estimate of overall survival (OS) by age group. There was no significant difference in OS between the two groups (5-year OS rate, 56.2% vs. 57.8%,  $p=0.78$ ). Median follow-up was 46 months

significant differences in OS ( $p=0.78$ ), with a 5-year OS rate of 56.2% 95% CI, 36.6–71.9%) in the elderly group and 57.8% 95% CI, 48.1–66.3%) in the younger group (Fig. 2).

### Univariate and multivariate analyses of prognostic factors associated with OS in stage II–IV patients

In the univariate analysis, PS of 2–4 ( $p < 0.001$ ), Stage III–IV ( $P = 0.002$ ), and suboptimal surgery ( $p < 0.001$ ) were associated with worse prognosis. In the multivariate analysis, PS of 2–4 (HR, 2.572; 95% CI, 1.397–4.737;  $p = 0.002$ ), Stage III–IV (HR 6.222; 95% CI 1.502–25.77;  $p < 0.011$ ) and suboptimal surgery (HR 2.229; 95% CI 1.338–3.712;  $p < 0.002$ ) were associated independently with worse prognosis (Table 6). Age  $\geq 70$  years was not an independent prognostic factor.

### Discussion

This study clarified the type of treatment received by ovarian cancer patients and, particularly, the proportion of elderly ovarian cancer patients receiving standard treatment compared with younger patients in Japan.

In this study, surgery was performed at a rate of 94.5% in elderly patients, similar to younger patients. This differs from several reports from Europe and the United States where the rate of ‘no treatment’ was more frequent in elderly patients than younger patients [15, 16]. Fourcadier et al. reported that 39.1% elderly patients aged  $> 70$  did not undergo surgery for treatment of their ovarian cancer [16]. The result of Gynecologic Oncology Group (GOG) 273 trial which explored the association between pre-treatment Instrumental Activities of Daily Living (IADL) and the patient’s ability to complete 4 cycles of chemotherapy

**Table 6** Univariate and multivariate analyses for overall survival in patients with Stage II or higher cancer

	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age						
≥ 70 years	1			1		
< 70 years	0.641	0.394–1.045	0.074	1.248	0.693–2.248	0.459
PS						
0–1	1			1		
2–4	2.897	1.582–5.304	< 0.001	2.559	1.390–4.710	0.002
FIGO stage						
II	1			1		
III–IV	8.498	2.081–34.70	0.002	6.442	1.550–26.76	0.010
Histology						
Serous/ endometrioid	1					
Clear/mucinous/adeno-carcinoma/ other	1.442	0.804–2.586	0.218			
Residual disease						
Optimal	1			1		
Suboptimal	2.599	1.570–4.302	< 0.001	2.207	1.325–3.675	0.002
Therapy						
Standard therapy	1					
Nonstandard therapy	0.931	0.549–1.580	0.7933			
RDI for ddTC						
≥ 80%	1					
< 80%	1.137	0.714–1.811	0.587			

HR hazard ratio, CI confidence interval, PS performance status, FIGO International Federation of Gynecology and Obstetrics, CA125 cancer antigen 125, RDI relative dose intensity, ddTC dose-dense TC

without dose reduction or > 7-days treatment delay for patients aged 70 years and older with primary ovarian, peritoneal, or fallopian tube cancer, showed that in the carboplatin/paclitaxel combination regimen cohort approximately 50% of patients received primary chemotherapy with 25% not having debulking surgery and in the carboplatin alone arm, almost 60% had primary chemotherapy and over 50% of these did not received debulking surgery while on trial [8]. There are several possible reasons why the rate of surgery in this study was higher than other reports, including the difference of rate of frail patients, medical background, and the difference of study design, such as multiinstitutional or single institutional study. Disappointingly, there was no report of elderly patients with ovarian cancer in Japan. To clarify the problem in debulking surgery for elderly patients with ovarian cancer in Japan, it will be important to accumulate information on elderly ovarian patients throughout Japan.

In this study, IDS was performed more frequently in elderly patients than in younger patients. The reasons for the higher rate of IDS may include issues with the more advanced stage, lower PS, and the needs for management of complications. In addition, there may also be factors of age. Rauh-Hain, et al. reported that factors associated with performing neoadjuvant chemotherapy included older age at diagnosis, more advanced stage, serous adenocarcinoma subtype, and stage IV disease in a multivariable model using the data of 22,962 patients with microscopically confirmed epithelial ovarian cancer aged 70 years or younger in National Cancer Data Base [17]. This report suggests that older age was an independent factor to select IDS. On the other hand, there was no difference in the quality of the cytoreductive surgery in both groups. In multivariate analysis in this study, poor PS, advanced stage and the quality of cytoreductive surgery were independent poor predictive factors for OS; age was not. This result

suggests that cytoreductive surgery is beneficial in elderly patients. However, disappointingly there was the limitation of our study, as we did not analyse the details for patients' characteristics and perioperative complications for surgery. Next research, we should clarify the more details of feasibility for operation.

There has been no randomized clinical trial targeted to elderly ovarian cancer patients to determine the best chemotherapy for this group. Most clinical trials in the ovarian cancer field have not set an upper age limit, indicating that elderly patients with ovarian cancer may receive the same chemotherapy as young patients. For example, ddTC therapy significantly prolonged survival over conventional TC in a Japanese trial, and a prolonged survival benefit was evident even after subgroup analysis based on age (60 years or more) [1, 18]. Moreover, our previous reports showed elderly patients (70 years or more) with good organ function could receive ddTC therapy with over 80% of RDI, with the same prognosis as young patients [4]. These results suggest that it is important to perform standard chemotherapy for elderly patients as well as younger patients. In our previous study [4], ddTC therapy was feasible for elderly patients except severe neuropathy. However, limitations of the previous our study included the possibility of selection bias, since we excluded patients with poor PS and severe comorbidities from receiving ddTC therapy. In fact, elderly patients generally have more comorbidities and worse organ function than younger patients and there are individual differences between elderly patients. Some elderly patients who were so-called potentially vulnerable or frail could not receive standard therapy. Such vulnerable or frail patients were recommended less toxic therapy or best supportive care. Our study showed elderly patients received standard therapy significantly less than younger patients. Particularly, more elderly patients with stage II–IV cancers received weekly TC than younger patients, despite the fact that we usually perform ddTC therapy as standard chemotherapy for ovarian cancer with stage II–IV in our hospital. The regimen was decided by the doctor after discussion with patients in clinical practice. Retrospectively, it was very difficult to clarify the reasons why the doctor chose the appropriate regimen for his or her elderly patient, because there were several factors that we were unable to assess. Geriatric assessment is considered one tool to assess the frailty of elderly patients. By accumulating information prospectively, it may become possible to choose the appropriate chemotherapy by including information on the assessment that has not been previously measured in retrospective studies. In European countries and the United States, several prospective trials using geriatric assessment have been carried out to determine the feasibility of chemotherapy for elderly ovarian cancer patients [5–8]. However, there has not been a prospective trial in Japan. Further studies should be conducted to develop an

assessment tool to clarify the appropriate cancer treatment suitable for elderly Japanese ovarian cancer patients.

RDI is one indicator for choosing an appropriate and feasible chemotherapy for elderly patients. There was no significant difference in RDI between the elderly group and the younger group. This result suggests that the appropriate chemotherapy was chosen for each elderly patient. Additionally, several reports suggest that decreased RDI was identified as one of the poor prognostic factors for adjuvant chemotherapy [19, 20]. According to previous reports for ovarian cancer, RDI should be maintained at more than 70% for ovarian cancer chemotherapy [19]. Our study showed that not only young but also elderly patients maintained an RDI of over 70% and there was no significant difference between the two groups. The presence of a multidisciplinary team comprising medical oncologists, gynecologic surgeons, oncology pharmacists and oncology nurses involved in the management of the patients could also contribute to the high RDIs observed. It is very difficult to provide standardization of medical environment; however, when deciding to perform chemotherapy, we should give optimal therapy and supportive care to patients, including the elderly.

Similar to previous studies, we showed here that the frequency of peripheral neuropathy was significantly higher and the frequency of febrile neutropenia tended to be higher in elderly patients than in younger patients [4, 21]. Peripheral neuropathy might be a serious adverse event that degrades the quality of life and activities of daily living for elderly patients. PTX is a key drug for ovarian cancer treatment. Various clinical trials have been conducted in the past, however, PTX and CBDCA combination therapy (TC) has remained the superior treatment. Weekly PTX and CBDCA therapy was not better than TC therapy [11]. Liposomal doxorubicin and CBDCA therapy also did not perform better than TC therapy [22] in an adjuvant setting. However, these regimens are less toxic compared with TC therapy [11, 23] and may be of benefit to elderly patients.

## Conclusions

By forming a clear picture of the characteristics of elderly ovarian cancer patients, it will be possible to choose the appropriate treatments including the appropriate chemotherapy for each elderly patient. We need to develop further studies should be conducted to develop an assessment tool to clarify the appropriate cancer treatment suitable for elderly Japanese ovarian cancer patients with feasible and beneficial outcome.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

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