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Prognostic value of histological type in stage IV ovarian carcinoma: a retrospective analysis of 223 patients

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Background: Patients with FIGO stage IV epithelial ovarian carcinoma have a poor but non-uniform prognosis. This study aimed to compare the survival of patients with serous or endometrioid tumours (S/E) and clear cell or mucinous tumours (non-S/E).

Methods: Data for 223 patients who underwent surgery between 1987 and 2010 and were diagnosed by centralized pathology review and were retrospectively analysed. The patients included 169 with S/E tumours and 54 with non-S/E tumours.

Results: The median overall survivals (OSs) of the S/E and non-S/E groups were 3.1 and 0.9 years, respectively ($P < 0.001$). Six patients (2.7%), all with non-S/E tumours, died within 6 weeks after the initial surgery. Multivariate OS analysis revealed that performance status, residual tumor, metastatic sites, no debulking surgery, and non-S/E tumours were independent poor prognostic factors. For patients with non-S/E tumours, prognosis was more favourable for single-organ metastasis, except for liver or distant lymph nodes, no residual tumor, and resection of metastasis (median OS: 4.1, 4.6, and 2.6 years, respectively).

Conclusions: In stage IV ovarian carcinoma, non-S/E tumours are associated with a significantly poorer prognosis and higher rates of early mortality compared to S/E tumours. Therefore, careful management and development of new strategies are required.

Epithelial ovarian cancer (EOC) is one of the most lethal gynaecological malignancies (Brun *et al*, 2000; Jemal *et al*, 2007). In fact, ~15% of patients with EOC are diagnosed as International Federation of Gynaecology and Obstetrics (FIGO) stage IV disease. In previous studies, the median overall survival (OS) of patients with stage IV EOC was 15–29 months, with an estimated 5-year OS of ~20% (Bristow *et al*, 1999; Akahira *et al*, 2001; Winter *et al*, 2008; Trope *et al*, 2012). Many authors have reported that a combination of aggressive cytoreductive surgery and platinum-based chemotherapy improves survival and delays recurrence in patients with advanced EOC (Trimble *et al*, 2000; Bristow *et al*, 2002; Crawford *et al*, 2005). Previous research has shown that performance status (PS), as categorised by the Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO), and the presence of residual tumours are well-known prognostic factors for OS of patients with stage IV cancer (Goodman *et al*, 1992;

Curtin *et al*, 1997; Bristow *et al*, 1999; Trope *et al*, 2012). Some authors have reported that radical debulking surgery (DS) or microscopic cytoreduction are the most important factors affecting survival, even for patients with stage IV disease (Bristow *et al*, 1999; Winter *et al*, 2008; Luyckx *et al*, 2012).

The survival of patients with stage IV EOC remains poor and is not uniform owing to various metastatic patterns, PS, or histological characteristics. The histologic types of EOC are diagnosed based on the morphological criteria (1971; Tavassoli, 2003), and chemosensitivity and biological characteristics vary among histological types (Baak *et al*, 1986). In particular, serous tumours, one of the most advanced forms of EOC, are highly chemosensitive, which appears to affect survival results. A number of reports comparing clear cell or mucinous tumours to other epithelial tumours have indicated that these tumours have a worse prognosis than others in advanced stages (Sugiyama *et al*, 2000;

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Hess *et al*, 2004). However, there are few detailed analyses concerning the survival of patients with clear cell or mucinous tumours because few of these tumours are stage IV.

The aim of our study was to analyse both long-term survival and early mortality of patients with stage IV EOC by comparing serous or endometrioid tumours (S/E) with clear cell, mucinous, or other tumours (non-S/E).

METHODS

Between January 1987 and December 2010, 2385 patients with EOC were registered and treated by the Tokai Ovarian Tumor Study Group of Nagoya University Hospital and affiliated hospitals. Approval from the Ethics Committee of our hospital was obtained before study registration. The patients were enrolled in this study based on medical data and the surgical specimens from affiliated institutions. The specimens were returned after a central pathological review. The review was performed by one fixed pathologist specializing in gynaecologic tumours. Since 2012, the central pathological review system had consisted of two fixed pathologists and one gynaecologic oncology specialist. When there was a different diagnosis between each hospital and the central review, we informed each institution of the results with detailed comments. If it was necessary to distinguish the histological type, we added the findings from the immunohistochemistry staining. When it was difficult to diagnose the histology in residual tumours because of the prior chemotherapeutic effect, it was identified as 'adenocarcinoma' or 'no residual cancer'. These cases were excluded from this study. A total of 244 (10.2%) of the 2385 patients were diagnosed with stage IV cancer by a central pathological review system. Of the 244 patients, those who had not undergone surgery and those lost to follow-up immediately after the initial treatment were excluded. Prognostic data from the remaining 223 patients were retrospectively evaluated by dividing the patients into two groups: 169 patients (75.7%) were in the S/E group, including 144 (64.5%) with serous tumours, and 54 patients (24.2%) were in the non-S/E group, including 23 (10.5%) with clear cell tumours, 16 (7.2%) with mucinous tumours, 7 (3.1%) with undifferentiated tumours, and 5 (2.2%) with unclassified tumours. Pathological staging was assessed according to the 1988 FIGO criteria (Rio de Janeiro, Brazil), TNM Classification of Malignant Tumours by the Union for International Cancer Control (UICC), and all tumours were histologically classified according to the WHO classification. Pure-type clear cell adenocarcinoma was pathologically diagnosed if typical clear cytoplasm or hobnail cells growing in a papillary, solid, or tubular-cystic pattern appeared in more than 90% of all pathological specimens.

DS consisted of total hysterectomy, bilateral salpingo-oophorectomy, and total/partial omentectomy with/without resection of the metastatic tumor or pelvic and para-aortic lymphadenectomy. Non-DS was defined as surgery other than DS, namely exploratory laparotomy or salpingo-oophorectomy for the diagnosis of cancer. Patients in the non-DS group had not undergone secondary DS because of progression of the disease. Interval DS (IDS) included DS after several cycles of neoadjuvant chemotherapy (NAC) with/without primary incomplete surgery. All 70 patients who had NAC without primary surgery had positive cytology of cancerous ascites/pleural effusion or carcinoma by biopsy of metastatic sites. Of the 70 patients, the presence of peritoneal dissemination beyond the pelvis was also examined by imaging analysis, such as computed tomography. The pathological diagnosis in these patients was performed using IDS specimens. The residual tumor was defined as the maximal tumor diameter at the time of surgery.

Patients who received adjuvant chemotherapy were divided into two groups, one receiving taxane-platinum therapy (TP) and the

other receiving platinum-based therapy. The TP group consisted of 122 patients who received paclitaxel (175–180 mg m⁻²) plus carboplatin (AUC 5–6), 4 who received docetaxel (70 mg m⁻²) plus carboplatin (AUC 5–6), and 2 others. Other platinum-based therapies were given to 91 patients, including 46 who received cyclophosphamide (300 mg m⁻²) plus cisplatin (70 mg m⁻²) with/without adriamycin (30 mg m⁻²); 17 who received bleomycin (12 mg m⁻²), vinblastine (6 mg m⁻²), and cisplatin (70 mg m⁻²); 18 who received carboplatin (300 mg m⁻²) plus cisplatin (70 mg m⁻²); and 12 others. Further details concerning the employed chemotherapy regimens have been documented in our previous report (Mizuno *et al*, 2006). Most responses to treatment in the recent cases were evaluated according to the Response Evolution Criteria in Solid Tumours (RECIST) guidelines. However, it was difficult to adapt the RECIST to the past cases; therefore, we defined this case, in which there were no disease findings based on imaging and tumor markers after initial treatment, as a complete response (CR); another case was identified as non-CR.

Survival was measured from the date of diagnosis until the date of death or of the final follow-up visit. OS curves were calculated using the Kaplan–Meier method, and significance was determined using log-rank tests. Multivariate analysis was performed using the Cox proportional hazards model to evaluate the effects of independent factors on survival. Categorical data, which were analysed using the chi-squared test or Fisher's exact test, were used for comparisons of our data, and *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using the IBM SPSS software package for Windows, version 21 (Armonk, NY, USA).

RESULTS

Patient characteristics. The characteristics of the patients with S/E and non-S/E tumours are summarised in Table 1. The median age at the time of diagnosis for patients with S/E tumours was 56.8 years, with a range of 30–79, and the median age at the time of diagnosis for patients with non-S/E tumours was 54 years, with a range of 18–78 (*P* = 0.309). The rate of IDS was significantly lower in the non-S/E group than in the S/E group (14 vs 46.1%, respectively). There were no significant differences in the rate of TP chemotherapy vs other platinum-based regimens that were used as first-line chemotherapy (*P* = 0.468). However, the four patients who had not undergone post-surgery chemotherapy because of complications belonged to the non-S/E group. The mean number of cycles of first-line chemotherapy was significantly lower for the non-S/E group than for the S/E group (5.1 cycles vs 6.98 cycles, respectively; *P* < 0.001). The data on the metastatic sites and on the resection of the metastatic sites for all cases are shown in Supplementary Table 1–2. Of the 31 cases involving lymph nodes, 90.3% (28 out of 31) exhibited metastasis to the supra-diaphragmatic lymph nodes. Forty-three patients had metastatic involvement of other single organs, including 12 lung, 10 umbilicus, 9 spleen, 5 breast, 3 bone, and 4 others (the data are shown in Supplementary Table 1). In terms of resection of metastatic sites, bowel surgery was performed in 22 patients, liver tumor extraction was performed in 5 patients, neck dissection was performed in 5 patients, splenectomy was performed in 4 patients, and pulmonary tumor extraction was performed in 3 patients (the data are shown in Supplementary Table 2).

OS. The median OS times of the S/E and non-S/E groups were 3.1 (95% confidence interval (CI), 1.9–3.2) and 0.9 (95% CI, 0.6–1.3) years, respectively (*P* < 0.001), and the 5-year OSs for these groups were 31 and 16%, respectively. The median OS according to histological type based on univariate analysis is shown in Table 2. The prognosis of the non-S/E group was significantly worse in relation to many variables, and the median OS for this group was

Variables	Number of patients (%)			P-value
	Total	S/E group ^a	non-S/E group	
Age (years)				
<60	146	109 (64.5)	37 (68.5)	0.626
≥60	77	60 (35.5)	17 (31.5)	
Performance status				
0–1	166	134 (79.3)	32 (59.3)	0.096
2–4	53	36 (21.3)	17 (31.5)	
Metastatic site				
Pleural effusion	89	68 (40.2)	21 (38.9)	0.128
Liver	31	24 (14.2)	7 (13.0)	
Lymph nodes	31	29 (17.2)	2 (3.7)	
Other single organ	43	30 (17.8)	11 (20.4)	
Multiple organs	29	18 (10.7)	9 (16.9)	
Stage^b				
pT1	11	7 (6.7)	4 (8.8)	0.816
pT2	18	12 (11.3)	6 (13.3)	
pT3	122	87 (82.0)	35 (77.7)	
Peritoneal dissemination beyond pelvis				
Yes	176	138 (81.7)	38 (70.4)	0.076
No	45	30 (17.8)	15 (27.8)	
Surgery				
Primary debulking surgery	91	65 (38.5)	26 (48.1)	<0.001
Interval debulking surgery	86	78 (46.2)	8 (14.8)	
Incomplete surgery ^c	46	26 (15.4)	20 (37.0)	
Lymphadenectomy^d				
Yes	65	52 (36.4)	13 (39.4)	0.883
No	112	91 (63.6)	21 (63.3)	
Resection of metastatic sites^d				
Yes	40	33 (23.1)	7 (21.2)	0.696
No	137	110 (76.9)	28 (84.8)	
Residual tumor				
No	51	42 (24.8)	9 (16.7)	0.076
<1 cm	21	19 (11.2)	2 (3.7)	
≥1 cm	151	108 (63.9)	43 (79.6)	
Regimen of first line				
Taxane-platinum	128	101 (59.8)	27 (50.0)	0.468
Other platinum based	91	68 (40.2)	23 (42.6)	
Cycles of first-line chemotherapy				
Mean (range)		6.98 (1–19)	5.1 (1–10)	<0.001
Serum CA125 (IU ml⁻¹)				
Median (range)		1790 (8–18290)	280 (32–9700)	<0.001
Ascites (ml)				
<1000	123	92 (54.4)	32 (59.3)	0.268
>1000	81	63 (37.3)	21 (38.9)	
Unknown	15	14 (8.3)	1 (1.9)	

Abbreviation: S/E = serous or endometrioid tumours. Small numbers of patients with unknown status are omitted.

^aS/E: serous or endometrioid tumours; non-S/E: clear cell, mucinous, and others tumours.

^bStage: the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours, pT, was the postsurgical histopathological classification based on the TNM staging system. The patient number did not include 70 patients who had not received surgical staging before chemotherapy.

^cExploratory laparotomy or salpingo-oophorectomy.

^dExcludes cases of incomplete surgery.

particularly low for patients who had metastases to multiple organs (OS 0.26 years), PS > 2 (0.5 years), and ≥ 1000 ml ascites volume (0.5 years). However, the survival of patients with non-S/E tumours was similar to that of those with S/E tumours according to each of the following factors: metastasis to other single organs, which was defined as metastasis other than pleural effusion or to the liver or distant lymph nodes (median OS: 4.1 vs 3.9 years, $P=0.871$); <1 cm residual tumor (4.6 vs 4.2, $P=0.258$); and resection of metastatic sites (4.2 vs 2.6 years, $P=0.258$). When analysing patients based on metastatic site, there were significant

Variables	Total number	Median overall survival (years)		P-value
		S-E group ^a	Non-S/E group	
Age (years)				
<60	146	3.4	1.1	<0.001
≥60	77	3.1	0.8	0.010
Performance status				
0–1	166	3.3	1.0	<0.001
2–4	53	2.1	0.5	0.027
Metastatic site				
Pleural effusion	89	3.4	0.7	<0.001
Liver or distant lymph nodes	62	2.6	1.1	0.004
Other single organs	43	3.9	4.1	0.871
Multiple organs	29	1.8	0.26	0.009
Stage^b				
pT1	11	3.4	(75%)	0.35
pT2	18	8.1	0.7	0.084
pT3	122	2.4	0.6	<0.001
Peritoneal dissemination beyond pelvis				
Yes	176	3.1	0.7	<0.001
No	45	3.3	1.4	0.377
Surgery				
Primary debulking surgery	91	3.7	1.4	0.195
Interval debulking surgery	86	3.6	1.1	0.008
Incomplete surgery ^c	46	1.4	0.6	<0.001
Lymphadenectomy^d				
Yes	65	2.8	1.1	0.459
No	112	3.8	1.4	0.005
Resection of metastatic sites^d				
Yes	40	4.2	2.6	0.258
No	137	3.4	1.3	0.023
Residual tumor				
No	51	4.1	4.6	0.581
<1 cm	21	3.9	1.4	0.046
≥1 cm	108	2.4	0.9	<0.001
Regimen of first line				
Taxane-platinum	128	3.6	1.4	0.033
Other platinum based	91	2.5	0.7	<0.001
Serum CA125 (IU ml⁻¹)				
<1000	112	2.2	0.9	0.025
≥1000	111	3.7	0.9	<0.001
Ascites (ml)				
<1000	124	3.4	1.1	0.011
≥1000	84	2.6	0.5	<0.001

Abbreviation: S/E = serous or endometrioid tumours. Small numbers of patients with unknown status are omitted.

^aS/E: serous or endometrioid tumours; non-S/E: clear cell, mucinous, and others tumours.

^bStage: the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours. Patient's number did not include 70 patients who did not receive surgery before neoadjuvant chemotherapy. 5-year OS rate on pT1 in non-S/E group was 75%.

^cExploratory laparotomy or salpingo-oophorectomy.

^dExcludes cases of incomplete surgery.

differences in OS for those in the non-S/E group who had metastasis to other single organs vs pleural effusion ($P=0.038$) and for those who had metastasis to other single organs vs to multiple organs ($P=0.020$), but there were no differences in OS in the S/E group based on metastatic site. Furthermore, the prognosis in each metastatic site was analysed for patients with residual tumor compared with patients without residual tumor (Figure 1). In the S/E group, there was a significant difference in other single organs between patients with residual tumor and those without residual tumor ($P=0.020$, Figure 1A), but there was no difference in

pleural effusion (Figure 1B). In the non-S/E group, although there was no significant difference in each metastatic site, the prognosis of other single organs was more favourable for no residual tumor (5-year OS: residual (+), 32% vs residual (-), 72%, $P = 0.549$, Figure 1A).

The median OSs for both TP and other platinum-based chemotherapy regimens were statistically lower in the non-S/E group than in the S/E group. However, in the non-S/E group, the prognosis of patients who received TP chemotherapy was significantly more favourable than that of patients who received other platinum-based regimens (median OS: 1.4 vs 0.7 years, respectively; $P = 0.017$; Figure 2A and B).

Multivariate analysis was performed to further assess the factors, and these results are shown in Table 3. The analysis indicated that age, PS, metastatic pattern, surgery, residual tumor, and histological type were all factors that predicted worse survival of patients with stage IV EOC. The presence of multiple metastatic sites, > 2 cm residual tumor, and non-S/E tumours were found to be the most powerful predictors of prognosis.

Recurrence-free survival. In terms of the response to initial treatment, CR was achieved by 73% of the 169 S/E patients and by 31.4% of the 54 non-S/E patients and non-CR occurred in 37% of the S/E and 68.6% of the non-S/E patients. The proportion of patients in the non-S/E group with CR was significantly lower than that of the S/E group ($P < 0.001$), but there was no significant difference in the CR survival curve, as shown in Figure 3A and B (median OS S/E 3.9 vs non-S/E 5.6 years, $P = 0.391$). Disease relapsed in 119 (83.8%) of 142 patients with an initial CR. In these patients, the interval between effect assessment and recurrence

ranged from 1 month to 6.4 years, and there was no difference in the median recurrence-free survival between the S/E and non-S/E groups (1.5 vs 1.4 years, respectively; $P = 0.74$).

Early death and treatment-related mortality. Table 4 presents data for 14 patients with early death, defined as death within 3 months after primary surgery. The rate of early death was higher in the non-S/E group than in the S/E group (78.5 vs 21.4%, respectively; $P < 0.001$). Death within 6 weeks occurred in 6 (2.7%) patients in the non-S/E group. With regard to perioperative-related mortality, one patient had a cerebral infarction immediately after surgery, and another patient who had undergone IDS died owing to a pulmonary embolism following surgery (not shown in Table 4).

DISCUSSION

The present study retrospectively analysed the largest series of patients with stage IV EOC by comparing histological tumor types. Univariate and multivariate analyses revealed that non-S/E tumours were associated with a significantly worse prognosis and higher mortality rates compared with S/E tumours. However, our data demonstrated that patients with non-S/E tumours had OSs similar to those of patients with S/E tumours in regards to no residual tumor and single metastatic site, except for liver and lymph nodes.

As described in the Introduction, the 5-year OS of patients with stage IV EOC is ~20% (Bristow *et al*, 1999; Akahira *et al*, 2001; Winter *et al*, 2008; Trope *et al*, 2012); however, our results indicated a slightly better OS for these patients, i.e., a 5-year OS of

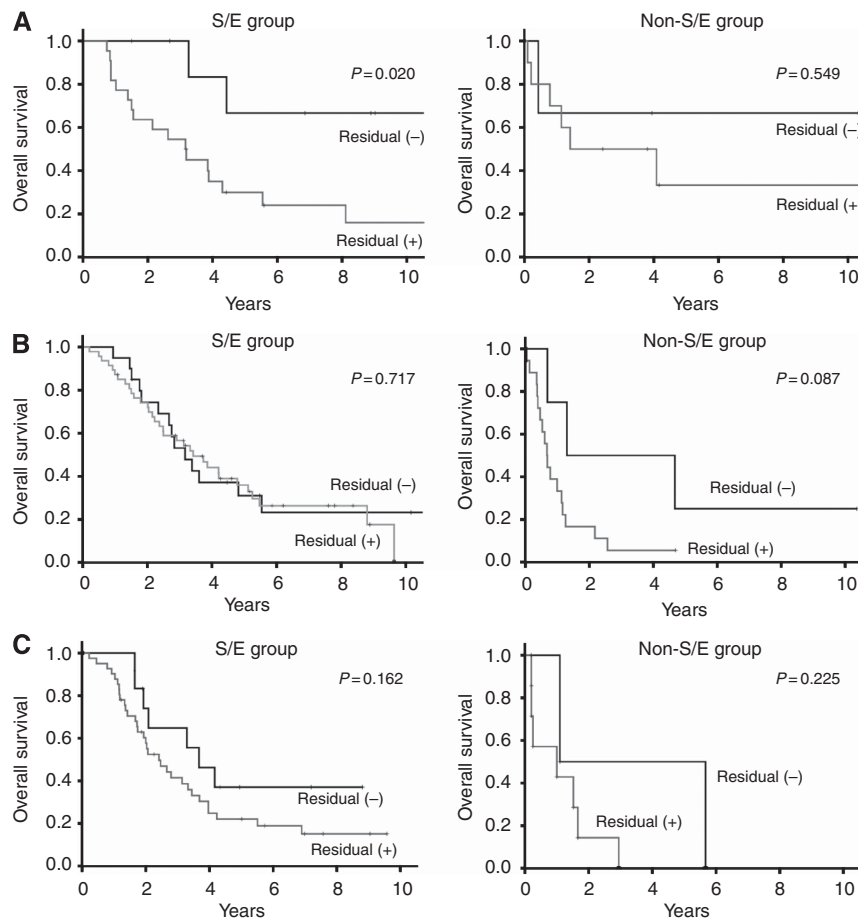


Figure 1. Overall survival curves according to the metastatic sites for stage IV patients either with residual tumor vs without residual tumor in each group; serous or endometrioid tumours (S/E group) and clear cell, mucinous, and other tumours (non-S/E group). (A) Other single organ, (B) pleural effusion, and (C) liver and lymph nodes.

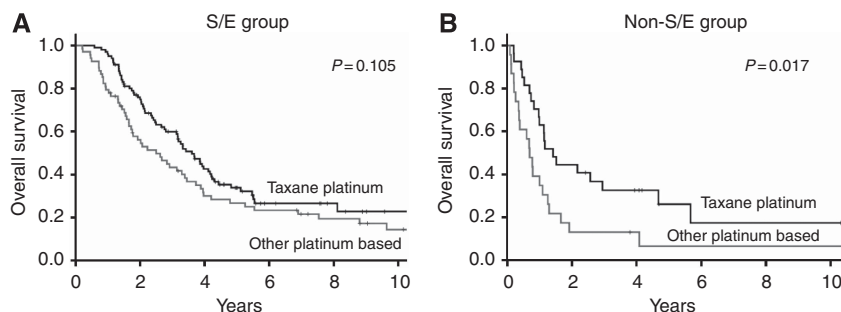


Figure 2. Overall survival curves according to chemotherapy regimen for patients with stage IV ovarian carcinoma. (A) S/E group, serous or endometrioid tumours; (B) non-S/E group, clear cell, mucinous, and others tumours.

Table 3. Multivariate analysis			
Variables	Hazard ratio	95% Confidence interval	P-value
Performance states			
0–1 vs 2–4	1.730	1.188–2.520	0.004
Metastatic site			
Other single organ ^a vs pleural effusion	1.674	1.038–2.701	0.035
Other single organ vs liver/lymph node	1.965	1.183–3.263	0.009
Other single organ vs plural organs	2.697	1.502–4.845	0.001
Surgery			
PDS vs IDS ^b	1.038	0.689–1.564	0.857
PDS vs incomplete surgery ^c	2.377	1.536–3.679	<0.001
Residual tumor			
No residual vs < 1 cm	1.889	1.047–3.411	0.035
No residual vs ≥ 1 cm	2.008	1.235–3.265	0.005
Histological type			
S/E group vs non-S/E group ^c	2.416	1.631–3.580	<0.001

Abbreviations: IDS=interval debulking surgery; PDS=primary debulking surgery.
^aOther single-organ metastasis does not include liver, distant lymph nodes, or pleural effusion.
^bIncomplete surgery consists of exploratory laparotomy or salpingo-oophorectomy.
^cS/E group, serous or endometrioid tumours; non-S/E group: clear cell, mucinous, and other tumours.

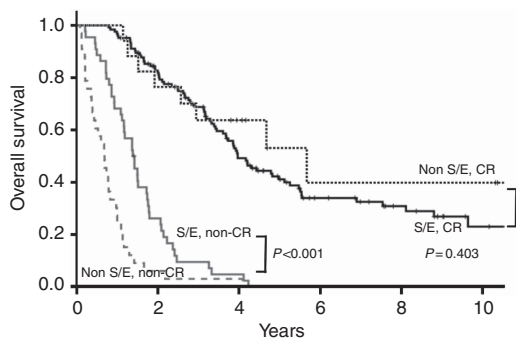


Figure 3. Overall survival curves according to the initial treatment response in patients with stage IV ovarian carcinoma. S/E group, serous or endometrioid tumours; non-S/E group: clear cell, mucinous, and other tumours; CR=complete response.

27.9% and a median OS of 30.8 months. Regarding histological type, many authors have demonstrated that clear cell or mucinous tumours have a significantly worse prognosis than other histologic types of stage IV EOC (Chan *et al*, 2008; Winter *et al*, 2008; Wimberger *et al*, 2010; Elstrand *et al*, 2012; Trope *et al*, 2012); the reported median OS ranges for serous tumours and clear cell tumours with or without mucinous tumor are 18.2–29.3 months and 6–14.2 months, respectively. Some multivariate analyses have demonstrated that clear cell/mucinous tumours are an independent prognostic factor (serous vs clear cell/mucinous tumours: hazard ratio (HR) 2.6, 95% CI 1.5–4.5, $P = 0.001$; Winter *et al*, 2008; Elstrand *et al*, 2012; Trope *et al*, 2012). However, in these reports,

the number of patients with these tumours was very small. Approximately 70% of patients with advanced-stage EOC have serous adenocarcinoma (McGuire *et al*, 1996; Chan *et al*, 2008), and both mucinous and clear cell adenocarcinomas are rare diseases. Previous research on stage IV EOC has demonstrated that ~2% (1.4–3%) of patients have clear cell tumours and that 4% (3.5–5.3%) have mucinous or clear cell tumours (Winter *et al*, 2008; Bamias *et al*, 2010; Rauh-Hain *et al*, 2012; Trope *et al*, 2012). Although Chan *et al* (2008) and other authors have reported that patients with clear cell tumours are more likely to be Asian (Mizuno *et al*, 2006; Chan *et al*, 2008), only a few reports have analysed stage IV EOC populations with a high percentage of clear cell (Akahira *et al*, 2001) or mucinous tumours (Wimberger *et al*, 2010). In this study, we analysed the prognostic factors of this disease by comparing the non-S/E group, which comprised 10.3% clear cell tumours, 7.2% mucinous tumours, and 3.1% undifferentiated tumours, with the S/E group, which included 64% serous tumours. By both univariate and multivariate analyses, the prognosis of the non-S/E group, which included a high percentage of clear cell tumours, was worse than that of the S/E group (HR 2.6, 95% CI 1.5–4.5, $P = 0.001$), as expected. In this study, we analysed clear cell, mucinous, and the other tumours as a group because there were no significant differences in the median OS of these histological types in the non-S/E group (clear tumor, 8.8 months; mucinous tumor, 11.3 months; and other tumours, 13.2 months).

Of the 14 patients who died within 3 months after primary surgery, 50% underwent primary DS (PDS) and 50% underwent incomplete surgery, as shown in Table 4. Eight (57.1%) of the patients with early death had PS of 0–1, and 6 (42.8%) had PS > 2. Notably, among 14 patients with early death, a significantly higher

Table 4. Early death and treatment-related mortality

Case	Age (years)	Histological type	Surgery	Metastatic sites	Ascites	Residual tumor	Chemo-therapy	Overall survival time (months)		Outcome
								Post surgery	Post chemo-therapy	
1	47	Clear cell	Salpingo-oophorectomy	Plural effusion	> 1000 ml	> 5 cm	None	0.3	—	CI
2	70	Clear cell	Exploratory laparotomy	Liver Pleural effusion	< 100 ml	1–2 cm	1 cycle	1.0	0.5	DOD
3	49	Mucinous	Salpingo-oophorectomy	Lung Vagina	500–1000 ml	> 5 cm	None	1.2	—	DOD
4	68	Clear cell	DS ^a + lymphadenectomy, bowel surgery	Liver Lymph nodes	> 1000 ml	> 5 cm	1 cycle	1.4	0.5	DOD
5	59	Clear cell	Exploratory laparotomy	Pleural effusion	> 1000 ml	> 5 cm	2 cycles	1.5	0.25	DOD
6	61	Clear cell	DS	Bone	> 1000 ml	< 1 cm	None	1.6	—	DOD
7	63	Endometrioid	DS	Liver	< 100 ml	> 5 cm	1 cycle	2.4	1.2	DOD
8	51	Clear cell	Salpingo-oophorectomy	Liver	100–500 ml	2–5 cm	1 cycle	2.4	1.4	DOD
9	37	Mucinous	Exploratory laparotomy	Pancreas	< 100 ml	> 5 cm	1 cycle	2.5	1.6	DOD
10	63	Serous	DS	Pleural effusion	100–500 ml	1–2 cm	2 cycles	2.5	0.5	DOD
11	58	Mucinous	Salpingo-oophorectomy	Liver Spleen	100–500 ml	> 5 cm	2 cycles	2.5	0.6	DOD
12	53	Serous	DS	Liver	> 1000 ml	> 5 cm	2 cycles	2.7	0.8	DOD
13	46	Mucinous	DS + lymphadenectomy	Liver Spleen	< 100 ml	> 5 cm	2 cycles	3.1	1.0	DOD
14	53	Undifferentiated	DS + lymphadenectomy	Liver	100–500 ml	1–2 cm	None	3.1	—	DOD

Abbreviations: CI = cerebral infarction; DOD = dead of disease; DS = debulking surgery.
^aDS consisted of hysterectomy, bilateral Salpingo-oophorectomy, and omentectomy.

proportion had non-S/E tumours compared with S/E tumours; 12 of the 14 patients had a non-S/E tumor, accounting for ~20% of the entire non-S/E group. Furthermore, after the initial chemotherapy, 5 (10%) patients in the non-S/E group died within 1 month, which suggested that there is an association between early death and poor chemosensitivity. Because clear cell tumours and mucinous tumours are less likely to respond to NAC than serous tumours, extended surgery should be considered as a first-line therapy for these tumor types.

However, our data indicated the possibility of long-term survival for some patients in the non-S/E group that had poor prognosis. The prognostic factors associated with these cases were residual tumor size, metastatic site, and TP chemotherapy. No research has analysed the prognostic factors in patients with only clear cell or mucinous tumours. Generally, for all stage IV EOC tumours, residual tumor size, PS, and completeness of the surgery are considered the most important prognostic factors that affect OS. Because the purpose of radical cytoreductive surgery is to retain as little gross tumor as possible, optimal surgery is the most important prognostic factor (Bristow *et al*, 2002; Winter *et al*, 2008; Vergote *et al*, 2010; Rauh-Hain *et al*, 2012). However, previous reports have differed in their definitions of optimal surgery depending on the amount of residual tumor. The median OS has been reported to be 34–64 months in patients with no residual tumours (Winter *et al*, 2008; Wimberger *et al*, 2010; Trope *et al*, 2012), ~38 months for those with <1 cm residual tumor (Bristow *et al*, 1999; Elstrand *et al*, 2012), and 25–40 months for those with <2 cm residual tumor (Liu *et al*, 1997; Akahira *et al*, 2001; Munkarah *et al*, 1997). In particular, some reports have shown a longer median OS of approximately 60 months for patients with no residual tumor (Winter *et al*, 2008; Wimberger *et al*, 2010). There are two possible reasons for this result: first, many of the enrolled patients might have had preferable conditions, such as good PS, because of the prospective study design for cytoreductive surgery in Stage IV EOC; second, the population included many patients with chemosensitive tumours rather than clear cell or mucinous

tumours. Our study also demonstrated a favourable prognosis for no residual tumor in both S/E (median OS, 49.2 months) and non-S/E groups (median OS, 55.2 months). In the non-S/E group, a good prognosis was also associated with resection of metastatic sites (Yes vs No: 2.6 vs 0.8 years, $P=0.258$). Furthermore, a favourable prognosis was also associated with metastasis to other single organ, such as the lung, spleen, or navel, especially, the OS rate was higher in patients with both factors; other single organ and no residual tumor (Figure 1A). These data suggest that complete cytoreductive surgery improves the prognosis of patients with resectable metastases, even if they have stage IV EOC. Previous studies of liver resection or diaphragm resection support these results (Bristow *et al*, 1999; Chereau *et al*, 2009). In a meta-analysis of patients with stage III or IV ovarian carcinoma, Bristow *et al* (2002) determined that maximal cytoreduction was one of the most powerful determinants of cohort survival. This group also found that consistent referral of patients with advanced ovarian cancer to expert centres for primary surgery may be the best currently available means for improving OS. In addition, there was no significant difference in pleural effusion between patients with residual tumor and without residual tumor in S/E group (Figure 1B). The possible reasons include that patients with pleural effusion had a high rate of IDS (67%) or a low rate of >2 cm residual tumor (13%) in the S/E group.

On the basis of the results of a large, randomized, phase III trial, paclitaxel-platinum therapy has been recommended as a first-line regimen for patients with advanced EOC (McGuire *et al*, 1996). In particular, incorporating paclitaxel into first-line therapy improves the duration of progression-free survival and OS in women with incompletely resected stage III and stage IV ovarian cancer. In the present study, although there were no significant differences in OS between TP chemotherapy and other platinum-based regimens in the S/E group, the OS rate for the non-S/E group was higher for TP chemotherapy than for other platinum-based regimens. The mean cycle number of first-line TP chemotherapy was significantly higher than that of other platinum-based regimens, and good

compliance with the continuation of TP therapy likely improves this prognosis. Despite good compliance, however, the survival of patients in the non-S/E group with TP chemotherapy was very poor compared with that of the S/E group. Our previous study of patients with recurrent ovarian cancer demonstrated that the prognosis of patients with non-clear cell/mucinous tumours was improved with TP chemotherapy (Kajiyama *et al*, 2014). The lack of a significant difference in survival according to type of chemotherapy in the S/E group may reflect the OS analysis rather than recurrence-free survival; these patients might have displayed different responses to treatment after initial chemotherapy in terms of recurrence.

Although the advantages of NAC-IDS have been discussed at length in studies comparing this treatment with PDS, PDS still remains the standard therapy for advanced EOC. Many authors have reported that NAC-IDS is associated with lower perioperative morbidity, a higher percentage of complete surgery without residual tumor, and similar survival (Hou *et al*, 2007; Vergote *et al*, 2010; Rauh-Hain *et al*, 2012). In our data, there was also no difference in survival between PDS and IDS (Table 3); however, the rate of early death or treatment-related mortality was much higher among patients who underwent PDS compared with IDS.

Our study has several limitations. Our results were obtained by retrospective analysis, and no details for older cases were available. All patients underwent surgery and pathological diagnosis, and patients who had received only chemotherapy were omitted. Although our patient population with clear cell or mucinous tumours was larger than those of previous studies, even larger studies are necessary because of the variable clinico-pathological characteristics of stage IV EOC patients. Although patients with stage IV EOC can expect long-term survival with active treatment, the general condition of these patients may be exacerbated by the treatment. Therefore, determining the proper treatment for stage IV patients with poor prognosis and poor PS is difficult, and those patients require adequate explanation of the available information to select the proper therapy.

CONCLUSION

In stage IV EOC, non-S/E tumours were associated with a significantly worse prognosis and higher rates of early mortality compared with S/E tumours. However, our data suggest that complete cytoreductive surgery improves the prognosis of patients with resectable metastases, not only for S/E tumours but also for non-S/E tumours. Therefore, the benefits and risks of aggressive surgery or palliative therapy in therapeutic management must be considered, and the development of new treatment strategies for these patients is required.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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