Int J Clin Oncol (2015) 20:143–149
DOI 10.1007/s10147-014-0687-1

ORIGINAL ARTICLE

Clinical features of long-term survivors of recurrent epithelial ovarian cancer

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Received: 11 November 2013 / Accepted: 12 March 2014 / Published online: 26 March 2014

Abstract
Background Although recurrent epithelial ovarian cancer (EOC) is generally regarded as an incurable disease, some patients survive more than 5 years after the first recurrence. The aim of this study was to evaluate the clinical features of patients with recurrent EOC who achieve long-term survival.
Methods We retrospectively reviewed the medical records of 164 patients with recurrent EOC and analyzed the clinical stage, histologic subtype, primary treatment, disease-free interval (DFI), recurrence site, secondary treatment, and overall survival from the time of the first recurrence (R-OS), using the Kaplan–Meier method and the log-rank test.
Results The median R-OS for all 164 patients was 25 months and the 5-year R-OS rate was 25.4 %. There were no significant differences in R-OS according to the disease stage. The median R-OS was significantly shorter in the 6–12-month DFI group (23 months) than in the ≥12-month DFI group (61 months) ($p = 0.0002$), while there was no significant difference between the 6–12 and 3–6-month DFI groups (20 months) ($p = 0.161$). Of the 164 patients, only 14 survived >5 years after the first recurrence. Most of them underwent surgery and/or radiotherapy in combination with chemotherapy and underwent >18 cycles of platinum-based chemotherapy throughout their treatments (median 22 cycles; range 4–44).
Conclusions If high sensitivity to platinum is maintained, patients with recurrent EOC may have prolonged survival following repeated platinum-based chemotherapy cycles. Moreover, their prognosis improves when chemotherapy is combined with secondary cytoreductive surgery and/or irradiation.

Keywords Recurrent epithelial ovarian cancer · Platinum-sensitivity · Disease-free interval · Long-term survival

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Introduction

Each year, approximately 8,000 women are diagnosed with ovarian cancer in Japan, and in 2007, 4,467 patients died of the disease [1]. Because the ovary is situated deep within the pelvic cavity, most patients do not notice the presence of a tumor, even if it becomes extremely large. In addition, there are no effective screening strategies for detecting early-stage ovarian cancer. Consequently, most patients are in advanced stages of the disease when they are diagnosed [2].

Most patients treated for epithelial ovarian cancer (EOC) experience a relapse, with a median progression-free survival period of 15–18 months, even if complete remission is achieved with the initial therapy, including both cytoreductive surgery and adjuvant chemotherapy [3, 4]. Importantly, 75–80 % of patients with advanced stages of EOC experience a relapse within 5 years of therapy initiation [2]. Systemic chemotherapy is the approved treatment for recurrent ovarian cancer, and the selection of antineoplastic agents depends on the patient's sensitivity to platinum-based chemotherapy drugs [4]. The response to

second-line chemotherapy generally correlates well with the length of the disease-free interval (DFI), which is defined as the time between the completion of the initial therapy and the diagnosis of recurrence [5]. If the DFI is ≥6 months, the recurrent disease is generally considered platinum-sensitive, while if the DFI is <6 months, it is considered platinum-resistant [5–8]. Patients with platinum-sensitive, recurrent cancer are recommended to receive repeated platinum-based combination regimens. However, the sensitivity of the cancer to platinum decreases with each subsequent relapse, and the DFI gradually shortens, with the cancer eventually becoming platinum-resistant. Therefore, recurrent disease is generally incurable, with the exception of a few fortunate patients.

Many clinical trials and retrospective studies have examined recurrent EOC, but there are few published reports summarizing long-term survival data after recurrence. The only summary data available come from studies examining the efficacy of surgical excision of localized disease [9–11] or the utility of secondary cytoreductive surgery (SCS) [12–17]. Most of these studies have suggested that complete tumor resection, rather than chemotherapy, is the most effective treatment for achieving long-term survival. In the present study, we summarized the characteristics of recurrent EOC patients with regard to their sensitivity to platinum-based chemotherapy and evaluated the factors contributing to an extended survival period.

Patients and methods

This study was approved by the ethics committee of the Cancer Institute Hospital (Tokyo, Japan). We reviewed the medical records of 596 EOC patients who were treated at our institute between 2000 and 2009, excluding 67 patients with synchronous or metachronous (within 5 years) malignancies other than in situ carcinoma and 11 patients with missing data, who were referred to another institution during their initial treatments. Of the remaining 518 cases, 258 patients (49.8 %) had suffered a relapse by June 2012, and we excluded the 94 patients who suffered relapses within 3 months of initial treatment despite aggressive initial treatments (i.e., those with persistent disease). Finally, we retrospectively reviewed the medical records of 164 patients and evaluated their International Federation of Gynecology and Obstetrics (FIGO) disease stages, histologic subtypes, primary surgeries, primary chemotherapies, DFIs, sites of recurrence, secondary treatments (surgery, chemotherapy, and radiotherapy), and outcomes.

Although the standard strategy for EOC treatment is primary cytoreductive surgery followed by adjuvant chemotherapy, we actively perform neoadjuvant chemotherapy followed by interval cytoreductive surgery and adjuvant chemotherapy for most advanced cancers with widespread invasive disease or poor performance status. Before 2005, first-line chemotherapy involved the use of ifosfamide, epirubicin, and cisplatin (IEP); after 2005, paclitaxel and carboplatin (TC) were used. For each of the 164 patients, we confirmed their complete remission following initial therapy and conducted regular follow-up examinations, including imaging and measurements of serum cancer antigen-125 (CA125) levels. Recurrence was defined as an increase in the CA125 levels to double the normal upper limit, the appearance of clinical symptoms, and/or the detection of measurable disease by imaging.

Upon recurrence, whether for the first time or subsequently, treatment involved systemic chemotherapy based on the patient's platinum-free interval (PFI): a platinum-based regimen was available for patients with a DFI >6 months in the absence of progressive disease or unacceptable toxicity and non-platinum regimens were employed when the DFI was <6 months. Thus, if the previous treatment for recurrence had resulted in complete response (CR) or partial response (PR) and no progression had occurred for >6 months, patients repeatedly received platinum-based regimens, as long as the DFI was >6 months at each subsequent relapse. If the site of recurrence was localized or became localized as a result of chemotherapy, surgery, and/or radiotherapy combined with chemotherapy was considered.

We classified the 136 cases, excluding 28 patients who never received platinum-based chemotherapy during their

Table 1 Clinical characteristics of patients with recurrent epithelial ovarian cancer

	All	Long-term survivors after first recurrence	
	($N = 164$)	>3 years ($N = 37$)	>5 years ($N = 14$)
Age (years)			
Median	56	55	55
Range	23–83	42–83	45–65
FIGO stage (no. of cases)			
I	27	9	4
II	16	5	2
III	99	23	8
IV	22	0	0
Histologic subtype (no. of cases)			
Serous	111	27	10
Clear	30	7	2
Endometrioid	6	3	2
Mucinous	2	0	0
Others	15	0	0

FIGO International Federation of Gynecology and Obstetrics, *DFI* disease-free interval

Table 2 Median overall survival from the first recurrence and the proportion of long-term survivors, according to DFI

DFI group	Median R-OS (months)	LTS-3 patients	LTS-5 patients
Res group ($N = 32$)	20	2/32 (6.3 %)	0/32 (0 %)
p-Sen group ($N = 44$)	23	7/44 (15.9 %)	1/44 (2.3 %)
h-Sen group ($N = 60$)	61	20/60 (33.3 %)	10/60 (16.7 %)

DFI disease-free interval, *R-OS* overall survival from the first recurrence, *LTS-3* patients who survived >3 years after the first recurrence, *LTS-5* patients who survived >5 years after the first recurrence, *Res* resistant, *p-Sen* partially sensitive, *h-Sen* highly sensitive

initial treatment, into the following 3 groups, according to their DFI: resistant (Res) ($n = 32$; DFI of 3–6 months), partially sensitive (p-Sen) ($n = 44$; DFI of 6–12 months), and highly sensitive (h-Sen) ($n = 60$; DFI $\geq$12 months).

The between-group differences were analyzed using chi-squared tests. Survival curves and rates were calculated using the Kaplan–Meier method; the differences in survival between each stage or each DFI group were evaluated using the log-rank test. A two-sided p value <0.05 was considered statistically significant. Statistical analyses were performed using R, version 3.0.0 (http://www.r-project.org/).

Results

Table 1 summarizes the clinical characteristics of the 164 patients who suffered relapses after complete EOC remission by June 2012. The median age of the patients was 56 years (range 23–83 years) and the median follow-up period was 42 months (range 4–150 months). According to the FIGO stage, 27 stage I cases, 16 stage II cases, 99 stage III cases, and 22 stage IV cases showed recurrence. Serous adenocarcinomas accounted for 67.7 % (111/164) of all of the histological subtypes.

Of the 164 patients suffering relapses, only 37 (22.6 %) survived >3 years after their first recurrence (LTS-3); 14 of those 37 patients (8.5 % of all patients with recurrence) survived for >5 years (LTS-5). The characteristics of the LTS-3 and LTS-5 patients are shown in Table 1. The median age of the patients in both the LTS-3 and LTS-5 groups was 55 years. The FIGO stages of the patients in LTS-3 and LTS-5 were stage I, 9 and 4 patients; stage II, 5 and 2 patients; and stage III, 23 and 8 patients, respectively. None of the patients with stage IV disease survived for >3 years. Serous adenocarcinomas accounted for 73.0 % (27/37) of the LTS-3 patients and 71.4 % (10/14) of the LTS-5 patients.

The proportions of LTS-3 and LTS-5 patients in the different DFI groups are presented in Table 2. Only 7 of 44

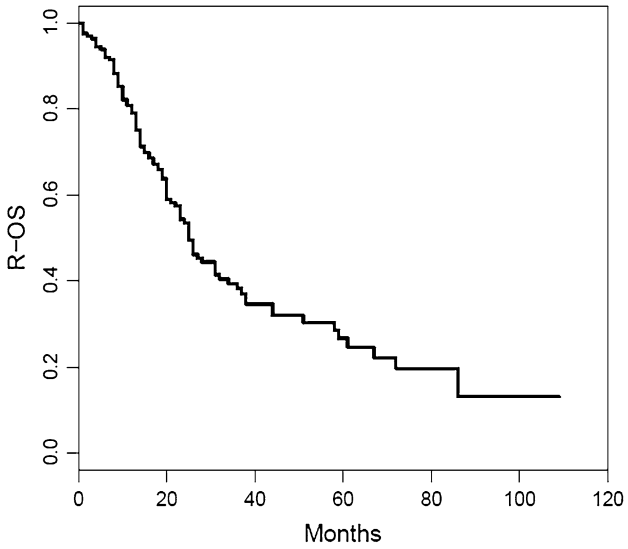

Fig. 1 Overall survival from the first recurrence (R-OS) for all 164 patients

p-Sen patients (15.9 %) survived for 3 years after the first recurrence, in contrast to 20 of 60 (33.3 %) h-Sen patients ($p = 0.076$). Moreover, among the patients surviving for at least 5 years after their first recurrence, the differences were more marked between the p-Sen and h-Sen groups (2.3–16.7 %; $p = 0.042$).

In 29 of 37 LTS-3 patients (78.3 %), peritoneal dissemination was detected at the time of the first recurrence. Of the 37 LTS-3 patients, 33 received treatment for recurrence at our hospital. Their treatment consisted of chemotherapy (11 patients), surgery (2 patients), chemotherapy and surgery and/or irradiation (18 patients), or best supportive care (2 patients). The 18 patients who received combination therapy achieved complete remission after successful localized therapy.

The median R-OS of the 164 patients was 25 months, and their 5-year R-OS rate was 25.4 % (Fig. 1). For each FIGO stage, the median R-OS times were 28 months (stage I), 26 months (stage II), 26 months (stage III), and 20 months (stage IV) (Fig. 2a); there were no significant differences according to stage ($p = 0.343$). The median R-OS in each DFI group was 20 months in the Res group, 23 months in the p-Sen group, and 61 months in the h-Sen group (Table 2; Fig. 2b). The median R-OS in the p-Sen group was significantly shorter than that in the h-Sen group ($p = 0.0002$), while there was no significant difference in the R-OS for the Res and p-Sen groups ($p = 0.161$).

Of the 37 LTS-3 patients, the median DFI and R-OS were 14 months (range 3–98 months) and 56 months (range 36–109 months), respectively. Table 3 shows the clinical courses of the LTS-5 patients, excluding 3 patients who never received platinum-based chemotherapy during

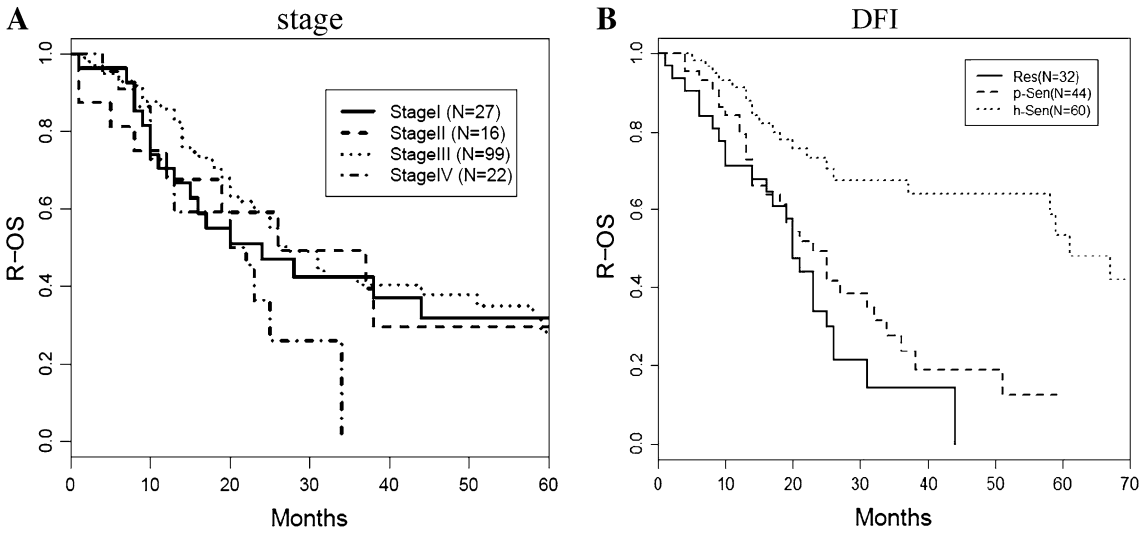

Fig. 2 Overall survival from the first recurrence (R-OS), according to (**a**) stage and (**b**) disease-free interval

their primary therapy because of early stage disease or non-serous histology.

The 3 excluded patients achieved long-term survival by means of chemotherapy and surgery (2 patients) or chemotherapy only (1 patient). Seven of the remaining 11 patients (63.6 %) were diagnosed with stage IIIC serous adenocarcinoma. The clinical courses of the 11 LTS-5 patients had 2 noteworthy features. First, 8 patients (72.7 %) received surgery and/or radiotherapy in combination with chemotherapy, as opposed to only 20 of the 150 non-LTS-5 patients. However, 7 LTS-5 patients had peritoneal dissemination at the time of recurrence, but achieved complete resection (CR) during surgery because their recurrent lesions had become localized as a result of chemotherapy. Second, 7 of 11 patients (63.6 %) received >18 cycles of platinum-based chemotherapy throughout their treatment for recurrence. The median number of platinum-based chemotherapy cycles achieved was 22 (range 4–44). Of these, 2 patients could not continue TC chemotherapy; one demonstrated an allergic reaction to carboplatin after 18 cycles and the other developed myelodysplastic syndrome (MDS) after 28 cycles of the TC regimen. In contrast, the median number of platinum-based chemotherapy cycles was 5 for the non-LTS-5 patients throughout their treatment for recurrence, as far as we examined.

Discussion

The prognosis of patients with recurrent EOC has been described by the results of several randomized trials, which had varying patient populations. The median overall survival (OS) was shown to be 30–35 months for platinum-sensitive recurrence [18, 19] and 9–14 months for platinum-resistant recurrence [20, 21]. Furthermore, in several studies that assessed the efficacy of SCS, the OS range was 18–61 months in optimal cases and 5–26 months in suboptimal cases 14–17]. Therefore, even if the definition of "long-term" is controversial, a 5-year survival after the first recurrence must be considered "long-term". Kajiyama et al. [22] recently reported a retrospective analysis of the long-term clinical outcomes of 603 patients with recurrent ovarian cancer and showed that the 5-year survival rate, after the first recurrence, was extremely poor (16.9 %). In contrast, we showed that the median R-OS of all 164 patients was 25 months, and the 5-year R-OS rate was 25.4 %. These differences might be due to our patient population being restricted to relatively recent (after 2000) cases and the exclusion of cases of persistent disease.

In the present study, only 37 (22.6 %) patients survived >3 years after their first recurrence despite aggressive treatment, including repeated platinum-based chemotherapy and/or surgical excision at optimal times, combined with irradiation. Furthermore, patients surviving >5 years accounted for 14 of the 37 LTS-3 patients. Therefore, among the 37 LTS-3 survivors, the median R-OS was remarkably long (56 months). Although recurrent EOC is an incurable disease, we confirmed that appropriate treatment can prolong the R-OS. In the current study, most patients who achieved long-term survival had advanced-stage disease, especially stage IIIC serous adenocarcinoma, with a DFI of >12 months. These results suggest that although we cannot cure patients with chemo-resistant peritoneal dissemination, we might be able to prolong the survival of patients who have isolated recurrence or chemo-sensitive dissemination, regardless of their initial disease stage; the R-OS in patients with recurrent EOC might be independent of the original FIGO stage.

Table 3 Clinical courses and treatments of long-term survivors of recurrent epithelial ovarian cancer

Case	Age (years)	Stage	Histologic subtype	Regimen and cycles of the initial chemotherapy	DFI (months)	All sites of recurrence	All treatments for recurrent disease			R-OS (months)	Outcome
							Chemotherapy (taxane/platinum regimen)	Chemotherapy (other platinum-based regimen)	Surgery and/or radiotherapy		
1	55	IC	Clear	TC×6	11	Peritoneal dissemination, lung	TC×4	–	Tumor resection (CR)	60	AWD
2	64	IIB	Endometrioid	TC×6	13	CA125↑, PAN	TC×24	–	–	61	DOD
3	52	IIIC	Endometrioid	IEP×2[a]	60	Peritoneal dissemination, Umbilicus	TC×6	–	Tumor resection (CR)	63	AWD
4	62	IIIC	Serous	IEP×6	27	Peritoneal dissemination, PLN	TC×18	–	Bowel resection (CR)	67	DOD
5	61	IIIC	Serous	IEP×5	13	Peritoneal dissemination	TP×5, TC×2	–	Splenectomy (CR)	72	DOD
6	48	IIC	Serous	CAP×5	67	Peritoneal dissemination	TC×5	–	Bowel resection (CR)	72	AWD
7	58	IIIC	Serous	IEP×6	31	Peritoneal dissemination, PLN	DP×4, TC×25	–	–	73	AWD
8	60	IIIC	Serous	IEP×2, TP×4, TC×3	14	Peritoneal dissemination, brain	TC×29	–	Brain irradiation, splenectomy (CR)	85	AWD
9	55	IIIC	Serous	IEP×1[a]	14	Peritoneal dissemination	TC×28	IEP×5	–	86	DOD
10	52	IIIC	Serous	IEP×5	19	Peritoneal dissemination, PLN	TC×11, DC×11	–	Pelvic irradiation	86	AWD
11	45	IIIC	Serous	IEP×4	27	Peritoneal dissemination	TC×37	IEP×7	Bowel resection (CR)	109	AWD

DFI disease-free interval, *R-OS* overall survival from the first recurrence, *CR* complete resection, *IEP* ifosfamide + epirubicin + cisplatin, *TP* paclitaxel + cisplatin, *DP* docetaxel + cisplatin, *CAP* cyclophosphamide + adriamycin + cisplatin, *TC* paclitaxel + carboplatin, *PLN* pelvic lymph node, *AWD* alive with disease, *DOD* death of disease

[a] Discontinuation due to complications

On the other hand, previous studies have reported that the DFI is an important prognostic factor for recurrent EOC [14–16, 22]. In the current study, the median R-OS in the h-Sen group was significantly longer than in the p-Sen and Res groups. Furthermore, among the LTS-5 patients, there was a more marked difference between the p-Sen and the h-Sen groups (2.3–16.7 %; $p = 0.042$). Although this study was based on a retrospective analysis at a single institution, the results of subset analyses from several clinical trials have also shown that the prognoses for patients in the p-Sen groups were not as good as those for patients in the h-Sen groups [18, 19, 23, 24]. However, the cutoff at 12 months remains controversial, and different strategies may be necessary for patients in the p-Sen groups.

Among the LTS-5 patients, the median number of platinum-based chemotherapy cycles was 22 (range 4–44). Not only did these patients exhibit long DFIs after their first remission, but they also retained high platinum sensitivities for prolonged periods after their first recurrences. Notably, 7 of 11 LTS-5 patients (63.6 %) received >18 cycles of platinum-based chemotherapy throughout their treatment, and 3 patients were long-term survivors following only chemotherapeutic treatment. In contrast, the median number of cycles of platinum-based chemotherapy was only 5 for the non-LTS-5 patients. Thus, long-term survival appears to be dependent on maintaining platinum sensitivity as long as possible after recurrence.

The significance of SCS in recurrent EOC patients has been previously reported. Onda et al. reported that SCS had a large impact on the survival of recurrent EOC patients with at least 3 of the following characteristics: (1) DFI >12 months, (2) the absence of liver metastasis, (3) a solitary tumor, and (4) tumor size <6 cm. Patients with at least 3 of these characteristics, who underwent SCS, had a median survival period of 47 months and a 5-year survival rate of 45.9 % after recurrence [12]. Chi et al. [13] proposed guidelines and selection criteria for SCS in patients with recurrent, platinum-sensitive EOC. In their analysis, a significant survival benefit was demonstrated for residual lesions measuring <0.5 cm (median survival period of 56 months). In all other published reports, a survival benefit for EOC patients undergoing SCS has been demonstrated if they showed an isolated recurrence and a DFI >12 months [10, 11, 16]. In our study, 9 of the 14 LTS-5 patients achieved prolonged R-OS or cure as a result of surgery and/or radiotherapy on localized lesions, in combination with chemotherapy. Therefore, there is no doubt that successful localized therapy (surgery and irradiation) contributes to prolonged survival in patients with recurrent EOC.

At present, 2 randomized SCS trials are underway. One is the DESKTOP III trial (Arbeitsgemeinschaft Gynäkologische Onkologie group), which is aimed at comparing SCS, followed by second-line chemotherapy, against chemotherapy alone in patients prospectively selected according to a score determined by the DESKTOP-OVAR trial [25]. The other is a Gynecologic Oncology Group trial of adjuvant chemotherapy, comprising carboplatin and paclitaxel with and without bevacizumab and/or SCS in patients with platinum-sensitive recurrent ovarian cancer, peritoneal cavity cancer, or fallopian tube cancer. The results of these trials are expected to provide more meaningful information about SCS.

In conclusion, our data suggest that if patients with recurrent EOC maintain high platinum sensitivity, they may have prolonged survival following repeated platinum-based chemotherapy. Moreover, the prognosis improves if chemotherapy is successfully combined with SCS and/or irradiation.

Conflict of interest The authors have no conflicts of interest to declare and no funding received for this work.

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