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Clinical Studies

Secondary cytoreductive surgery for recurrent epithelial ovarian carcinoma: proposal for patients selection

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The value of secondary cytoreductive surgery (SCS) for recurrent ovarian cancer is still controversial. The aim of this study was to clarify candidates for SCS. Between January 1987 and September 2000, we performed SCS in 44 patients with recurrent ovarian cancer, according to our selection criteria, disease-free interval (DFI) >6 months, performance status <3, no apparent multiple diseases, age <75years and no progressive disease during preoperative chemotherapy, if undertaken. The variables were investigated by univariate and multivariate analyses. Of 44 patients, 26 (59.1%) achieved complete removal of all visible tumours at SCS. Secondary cytoreductive surgery outcome, complete or incomplete resection, was significantly related to overall survival ($P=0.0019$). As for variables determined before SCS, DFI >12 months, no liver metastasis, solitary tumour and tumour size <6 cm were independently associated with favourable overall survival after recurrence in the multivariate analysis. Patients with three or all four variables ($n=31$) had significantly better survival compared with the other patients ($n=13$) (47 *vs* 20 months in median survival, $P<0.0001$). In these patients, fairly good median survival (40 months) was obtained even in patients with incomplete resection. Secondary cytoreductive surgery had a large impact on survival of patients with recurrent ovarian cancer when they had three or all of the above-mentioned four factors at recurrence. These patients should be considered as ideal candidates for SCS.
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Since Griffiths (Griffiths, 1975) first demonstrated the inverse relationship between residual tumour size after primary debulking and survival of ovarian cancer patients in 1975, many investigators have reproduced and confirmed this observation (Hacker *et al*, 1983; Vogl *et al*, 1983; Delgado *et al*, 1984; Conte *et al*, 1985; Louie *et al*, 1986; Neijt *et al*, 1987; Hainsworth *et al*, 1988; Sutton *et al*, 1989). Thus, the value of debulking of large tumour masses in the primary surgery of ovarian cancer has been generally accepted, and primary cytoreductive surgery followed by chemotherapy is considered to be a standard treatment procedure for patients with advanced ovarian cancer.

The cytoreduction contributes to removal of the tumour burden and relief of symptoms caused by tumours or massive ascites. In addition, the cytoreduction has another important effect on the sensitivity to postsurgical chemotherapy. By removing bulky tumours, the decreased growth fractions should increase (Norton and Simon, 1977) and poorly perfused anoxic cells should decrease. By reducing the number of cancer cells, the chance for cancer cells to undergo spontaneous mutations resulting in drug resistance should decrease (Goldie and Coldman, 1979). All these effects are believed to enhance the sensitivity to chemotherapy.

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Theoretically, the favourable effects of cytoreduction may also be expected in patients with recurrent ovarian cancer. Recently, several investigators have reported the significant value of secondary cytoreductive surgery (SCS) in a subset of patients with recurrent ovarian cancer (Jänicke *et al*, 1992; Eisenkop *et al*, 1995, 2000; Vaccarello *et al*, 1995; Cormio *et al*, 1999; Zang *et al*, 2000, 2004; Munkarah *et al*, 2001; Scarabelli *et al*, 2001; Tay *et al*, 2002). The value of complete resection at the time of SCS for highly selected patients is in consensus in these recent reports. They reported a considerable number of factors related to good prognosis including longer disease-free interval (DFI), smaller size of residual tumour at primary cytoreductive surgery, good response to first-line chemotherapy, younger age at recurrence and smaller size of maximum tumour at recurrence. However, there is limited information regarding the ideal candidates for SCS. Although only preoperative or intraoperative variables before starting SCS should be analysed for selection of the candidate, these variables have been analysed together with SCS outcome in most previous studies. In addition, the follow-up periods of living patients were rather short (the median or average follow-up periods were between 1 and 4 years) (Jänicke *et al*, 1992; Vaccarello *et al*, 1995; Cormio *et al*, 1999; Zang *et al*, 2000, 2004; Munkarah *et al*, 2001; Scarabelli *et al*, 2001) in most of the previous reports.

Since 1987, we have performed SCS according to our criteria of patient selection in 44 out of 70 ovarian cancer patients who had recurrence after DFI. In the present study, the median follow-up

period of living patients is 60 months after the initiation of treatment, SCS or chemotherapy before SCS, for recurrence. Using univariate and multivariate analyses of variables before starting SCS, we planned to clarify the ideal candidates for SCS among patients with recurrent ovarian cancer.

PATIENTS AND METHODS

Patient selection

Between January 1984 and December 1999, we treated 236 patients with stage I to IV epithelial ovarian cancer at the Department of Obstetrics and Gynecology, University of Tokyo Hospital. Our standard surgical procedures for ovarian cancer consist of total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic or total omentectomy, and in advanced cases, debulking of tumour masses with maximum efforts. Patients with no or small intraperitoneal residual tumours (less than 2 cm in diameter) also underwent systematic retroperitoneal lymphadenectomy. The extent of retroperitoneal lymphadenectomy is pelvic lymph nodes only (1984–1986) or both pelvic and aortic lymph nodes (1987–1999). All but stage Ia patients underwent at least six cycles of cisplatin-based chemotherapies following surgery as described previously (Onda *et al*, 1998). Of the 236 patients, 204 (86%) achieved complete clinical remission after primary treatment.

By September 2000, 70 of the 204 (34%) patients had recurrence and, from January 1987 to September 2000, 44 of the 70 (63%) patients underwent SCS prior to or following chemotherapy. Administration of chemotherapy before SCS was decided based on various clinical factors including short DFI (DFI <12 months) and poor performance status (PS 3) defined by ECOG (Eastern Cooperative Oncology Group). Our selection criteria for SCS were as follows: (1) DFI >6 months, (2) age at recurrence <75 years, (3) PS 0–2 just before the surgery, (4) absence of apparent extensive intraperitoneal dissemination or multiple distant metastases and (5) no progressive disease during presurgical chemotherapy, if undertaken. There were three exceptions to the above-mentioned criteria for SCS. One patient with DFI <6 months (5 months) underwent SCS, because the recurrent site was expected to be limited to a solitary aortic lymph node by CT. The other two patients had PS 3 at surgery. One patient with three metastatic brain tumours underwent emergent brain surgery followed by γ-knife radiosurgery to one residual tumour (Kawana *et al*, 1997), and one patient underwent ileocaecal resection because of acute bowel obstruction. Before the treatment, informed consent was obtained from all of the patients.

Chemotherapy

Of 44 patients, 21 (47.7%) received chemotherapy before SCS and all of 44 patients were treated with chemotherapy after SCS. In all, one to eight (median: 2) cycles of presurgical chemotherapy were performed in eight of 13 (61.5%) patients with DFI <12 months and 13 of 31 (41.9%) patients with DFI >12 months. In total, 44 patients received two to nine (median: 4) cycles of postsurgical chemotherapy.

In all, two to four cycles of presurgical chemotherapy were generally administered until beneficial response (partial or minor response) was observed. In two patients, second-line chemotherapy showed no beneficial response, and SCS was performed after successful third-line chemotherapy (seven and eight cycles in total). One patient received only a cycle of presurgical chemotherapy, because SCS could not be scheduled immediately after diagnosis of recurrence.

The number of postsurgical chemotherapy given was determined by SCS outcome and response to chemotherapy, evaluated by CT scan and serum level of CA125. Generally, three to four cycles of chemotherapy were planned for patients with no residual tumour and five to six cycles of chemotherapy were planned for patients with any residual disease. In principle, we gave at least two cycles of chemotherapy after the serum level of CA125 was normalised. Thus, three patients were treated with more than six cycles of chemotherapy after SCS. On the contrary, chemotherapy was discontinued before accomplishment of the planned cycles in five patients because rapid disease progression or severe adverse effects were observed during the planned cycles.

In presurgical and postsurgical chemotherapies, a platinum-based combination, CAP, EP or TJ, was used. The CAP regimen consisted of 600 mg m^{-2} of cyclophosphamide, 30 mg m^{-2} of doxorubicin and 50–75 mg m^{-2} of cisplatin. The EP regimen consisted of 80 mg m^{-2} of etoposide during days 1–5 and 75 mg m^{-2} of cisplatin. Paclitaxel was introduced in Japan in 1998 and, thereafter, a TJ regimen consisting of paclitaxel (175 mg m^{-2} over 3-h infusion) and AUC 5 of carboplatin was used as second-line chemotherapy.

Statistical methods

Survival was measured from the day of starting treatment for recurrence, that is, the day of starting presurgical chemotherapy or the day of performing SCS. The survival curves were determined by the Kaplan–Meier product limit method (Kaplan and Meier, 1958). Factors influencing survival were analysed using the log-rank test (univariate) and Cox's proportional-hazards regression analysis (multivariate). These analyses were performed using a JMP program (SAS Institute Inc., USA). Contingency table analysis was performed using the χ^2 test or χ^2 test for trend.

RESULTS

Patient characteristics

The number of patients was three in stage I, two in stage II, 36 in stage III and three in stage IV according to the International Federation of Gynecology and Obstetrics (FIGO). Histology was serous type in 35, clear-cell type in three, endometrioid type in three, transitional cell type in two and mixed epithelial type in one. Median DFI was 18.5 months with a range of 5–58 months: one patient (2.3%) had 5 months, 12 (27.3%) had 6–12 months and 31 (70.5%) had >12 months. Median age at recurrence was 52 years with a range of 37–74 years. Median follow-up period of patients, excluding those who died, was 60 months with a range of 17–199 months from the initiation of treatment for recurrence.

Surgery

Our attempt to perform SCS resulted in exploratory laparotomy in four patients (9.1%) due to the presence of unexpected extensive peritoneal tumours. Various debulking surgeries classified into four categories such as (1) gastrointestinal resection, (2) resection of other organs, (3) lymph node dissection and (4) other tumour debulking was performed with maximum efforts in the remaining 40 patients (90.9%). Among these patients, gastrointestinal resection (category 1) was required in 11 patients (25.0%), large bowel resection in nine patients (20.5%), small bowel resection in three patients (6.8%), partial gastrectomy in one patient and ileocaecal resection in one patient (2.3%), and one of the patients (2.3%) underwent sigmoid colostomy. Three patients had category 1 surgeries at two sites. Resection of other organs (category 2) was required in six patients (13.6%), splenectomy in three patients (6.8%), distal pancreatectomy in two patients (4.5%), partial liver resection in one patient, hysterectomy in one patient and brain tumour resection in one patient (2.3%). Two patients had category 2 surgeries at two sites. Regional or distant lymph node dissection (category 3) was performed in 12 patients (27.3%). Five patients

(11.4%) underwent systematic aortic lymphadenectomy and one (2.3%) underwent both systematic pelvic and aortic lymphadenectomies. Selective dissections of the following lymph nodes were performed in six patients: aortic nodes in one patient, pelvic nodes in one patient, axillary nodes in one patient, portal nodes in one patient, inguinal nodes in one patient and mesenteric nodes in one patient (2.3%). Other tumour debulking (category 4) including removal of tumours in the remnant omentum, the diaphragmatic muscles and vaginal stump, and tumours on the visceral or parietal peritoneum including the under surface of the diaphragm, was performed in 22 patients (50.0%); omentectomy in seven patients; partial full-thickness diaphragm resection in one patient; resection of tumours around the vaginal stump in four patients (9.1%); peritoneum resection of disseminated tumours on the under surface of the diaphragm; and other peritoneal surfaces in 16 patients (36.4%). Six patients were counted twice because they underwent two types of category 4 surgeries. In all, 10 patients underwent two or three out of the above four categories of debulking surgery. No patients died within a month following SCS.

Cytoreductive outcome and survival of patients

Among a total of 44 patients, complete resection of visible tumours was achieved in 26 patients (59.1%), largest residual tumours <1 cm in diameter were left in 11 patients (25.0%) and largest residual tumours $\geqslant 1$ cm in diameter were left in seven patients (15.9%). The median survival and 5-year survival of all patients who underwent cytoreductive surgery were 32 months and 33.2% (Figure 1), whereas the median survival and 5-year survival of 26 patients who had recurrence after complete remission achieved by primary treatment and did not undergo the surgery were 11 months and 3.9%. Figure 2 shows the survival of patients after the initiation of treatment for recurrence according to the outcome of SCS (SCS outcome). The median survival and 5-year survival after recurrence of the patients with largest residual tumours 0, <1 and $\geqslant 1$ cm were 52 months and 47.6%, 23 months and 18.2% and 20 months and 0%, respectively ($P=0.0007$, log rank). The overall survival of patients with no residual tumour was much better than that of patients with residual tumours (22 months in median survival and 12.0% in 5-year survival, figure not shown) with statistical significance ($P=0.0019$). There was no statistical difference in overall survival between patients with residual tumours <1 and $\geqslant 1$ cm ($P=0.1314$).

Factors influencing survival in univariate analyses

Factors influencing overall survival after recurrence were analysed using univariate analyses. Factors analysed and the results of univariate analyses are listed in Tables 1 and 2. As for prognostic factors determined during primary therapy, univariate analyses revealed that peritoneal tumour spread ($P=0.039$), FIGO stage ($P=0.045$) and aortic lymph node metastasis ($P=0.009$) were significantly associated with overall survival after recurrence. Regarding prognostic factors determined at recurrence, univariate analyses revealed that DFI ($P=0.002$), presence of liver metastasis ($P=0.005$), number of recurrent tumours ($P=0.007$), size of maximum tumour ($P<0.001$) and SCS outcome ($P=0.002$) had significant associations with overall survival after recurrence.

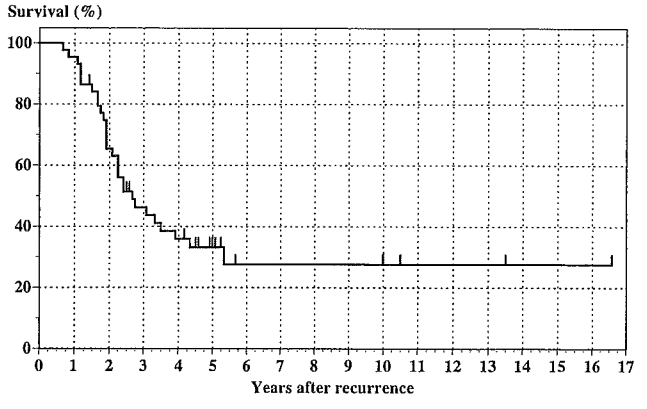

Figure 1 Survival of all 44 patients who underwent SCS.

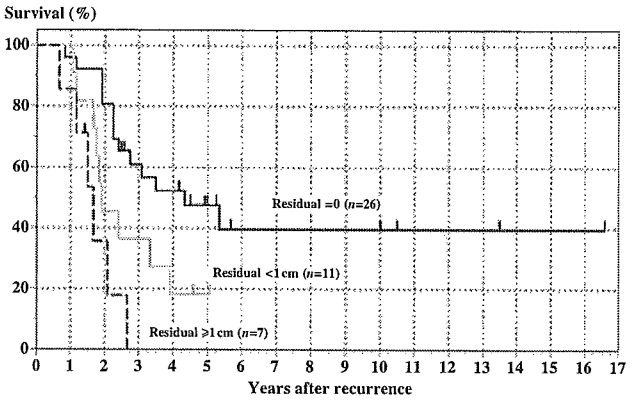

Figure 2 Outcome of SCS and survival. Survival of the patients with largest residual tumours 0, <1 and $\geqslant 1$ cm is shown in solid black, solid grey and dotted black line, respectively. The difference of survival is statistically significant ($P=0.0007$, log rank). There is no statistical difference in survival between patients with residual tumours <1 and $\geqslant 1$ cm ($P=0.1314$, log rank).

Table 1 Univariate analyses for variables during primary treatment

Variables	Number	Median survival (months)	P-value
Peritoneal tumour spread			
Localised to the pelvis	10	NA	
Extended beyond the pelvis	34	29	0.039
Stage			
I/II	5	NA	
III/IV	39	29	0.045
Aortic lymph node metastases			
Absent	25	64	
Present	14	27	
Not assessed	5	25	0.009
Pelvic lymph node metastases			
Absent	20	47	
Present	21	32	
Not assessed	3	25	0.126
Systematic lymphadenectomy			
Not performed	3	25	
Pelvic only	7	29	
Pelvic and aortic	34	33	0.296
Histology			
Serous	35	37	
Others	9	23	0.197
Residual tumour at PCS			
0	34	32	
Any	10	40	0.961

PCS = primary cytoreductive surgery; NA = not applicable.

Table 2 Univariate analyses for variables at recurrence

Variables	Number	Median survival (months)	*P*-value
Age at recurrence (years)			
<50	17	29	
⩾50	27	40	0.860
Disease-free interval (months)			
⩾12	31	47	
<12	13	23	0.002
Intraperitoneal tumour			
Absent	12	64	
Present	32	27	0.117
Pelvic or aortic lymph node metastases			
Absent	34	32	
Present	10	37	0.419
Distant metastasis			
Absent	38	32	
Present	6	40	0.496
Liver metastasis			
Absent	42	33	
Present	2	20	0.005
No. of recurrent tumours			
Solitary	16	64	
Multiple	28	27	0.007
Size of maximum tumour (cm)			
<6	38	40	
⩾6	6	14	<0.001
Massive ascites (>500 ml)			
Absent	41	33	
Present	3	32	0.318
PS			
0–2	42	29	
3	2	42	0.746
Presurgical chemotherapy			
Not done	23	33	
Done	21	29	0.677
Bowel resection			
Not done	33	33	
Done	11	27	0.650
Residual tumour at SCS			
0	26	52	
Any	18	22	0.002

PS = performance status; SCS = secondary cytoreductive surgery.

Factors influencing survival in multivariate analysis

To determine patient selection for the surgery, we performed multivariate analysis using statistically significant prognostic factors in univariate analyses. Out of eight significant factors, SCS outcome was omitted in the multivariate analysis because SCS outcome is not yet known on considering indications for the surgery, although SCS outcome had a statistically significant correlation with the number of recurrent tumours ($P<0.001$, χ^2 test). The multivariate analysis using the remaining seven factors revealed that four factors determined at recurrence, specifically DFI, presence of liver metastasis, number of recurrent tumour and size of maximum tumour, were independently and significantly associated with survival after recurrence (Table 3). Additionally, the multivariate analysis using only these four factors confirmed

Table 3 Multivariate analysis using the seven prognostic variables in the univariate analyses

	Multivariate analysis	
Variables	**Risk ratio (95% CI)**	***P*-value**
Peritoneal tumour spread at PCS		
Localised to the pelvis	1.00	
Extended beyond the pelvis	0.80 (0.42–1.76)	0.540
Stage		
I/II	1.00	
III/IV	0.90 (0.22–5.60)	0.893
Aortic lymph node metastases at PCS		
Absent	1.00	
Present	1.23 (0.56–2.64)	
Not assessed	1.78 (0.61–5.33)	0.088
Disease-free interval (months)		
⩾12	1.00	
<12	2.45 (1.11–5.39)	0.027
Liver metastasis		
Absent	1.00	
Present	4.00 (1.40–10.03)	0.013
No. of recurrent tumours		
Solitary	1.00	
Multiple	3.73 (1.79–9.58)	<0.001
Size of maximum tumour (cm)		
<6	1.00	
⩾6	7.43 (3.12–18.92)	<0.001

PCS = primary cytoreductive surgery.

that all four factors were independently and significantly associated with survival after recurrence. The relative risk (95% confidence interval) was 0.37 (0.20–0.68) for DFI >12 months, 0.23 (0.10–0.65) for absence of liver metastasis, 0.26 (0.12–0.48) for a solitary tumour and 0.20 (0.09–0.42) for size of maximum tumour <6 cm.

Grouping of patients determined by the number of favourable prognostic factors

According to the number of favourable statuses among the above-mentioned four prognostic factors, that is, DFI >12 months, no liver metastasis, solitary tumour and tumour size <6 cm, patients were divided into four groups as follows: patients with all four favourable factors (Group 4, $n=10$), patients with three favourable factors (Group 3, $n=21$), patients with two favourable factors (Group 2, $n=11$) and patients with only one favourable factor (Group 1, $n=2$). There were no patients with zero favourable factors. Complete resection of visible tumours was achieved in 100% (10 of 10), 62% (13 of 21), 18% (two of 11) and 50% (one of two) of patients in Group 4, Group 3, Group 2 and Group 1, respectively. Apparently, a higher rate of complete surgical resection was achieved in patients with a larger number of favourable factors, and the distribution was statistically significant by contingency table analysis ($P<0.001$, χ^2 test for trend). The 5-year survival of Group 4 was 88.9% and median survival was not reached. The 5-year survivals and median survivals of Group 3, Group 2 and Group 1 were 26.0, 0 and 0%, and 37, 20 and 10 months, respectively (figure not shown). The differences of overall survival were also statistically significant among the four groups ($P<0.001$, log rank) and between them (e.g. $P<0.007$ in Group 1 *vs* Group 2, $P<0.001$ in Group 2 *vs* Group 3 and $P<0.001$ in Group

3 *vs* Group 4, log rank). Figure 3 shows the combined survival of Group 4 and Group 3 and that of Group 2 and Group 1. Patients with three or all four favourable factors (Group 3/4) ($n=31$) had significantly better survival compared with those with less than three favourable factors (Group 1/2) ($n=13$) (median and 5-year survival; 47 months and 45.9% *vs* 20 months and 0%, $P<0.001$).

Survival of patients determined by the number of favourable prognostic factors and SCS outcome

Patients with three or all four favourable prognostic factors (Group 3/4) had better survival when complete surgical resection was achieved at the time of SCS ($n=23$) (64 months in median survival, 53.8% in 5-year survival). However, even when SCS left residual tumours, survival of the Group 3/4 patients ($n=8$) was fairly good (40 months in median survival, 25% in 5-year survival). On the other hand, Group 1/2 patients had poorer survival both in completely resected cases ($n=3$) and in incompletely resected cases ($n=10$) (23 and 18 months in median survival, and 0 and 0% in 5-year survival) (Figure 4).

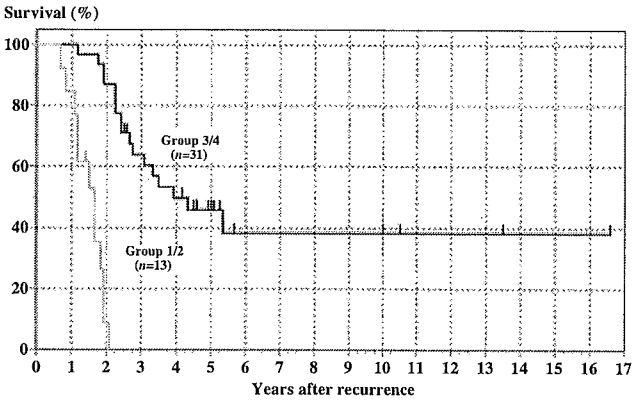

Figure 3 Comparison in survival between patients having one or two favourable prognostic factors (Group 1/2) and three or four favourable factors (Group 3/4). Survival of patients in Group 3/4 and Group 1/2 is shown as a solid black or solid grey line, respectively. Patients in Group 3/4 had significantly better survival compared with patients in Group 1/2 ($P<0.001$, log rank).

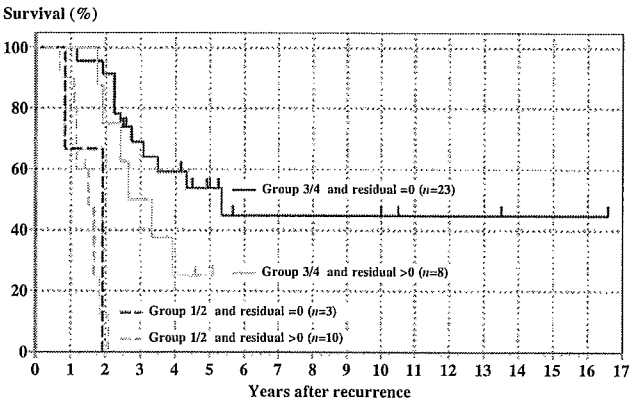

Figure 4 Survival in relation to SCS outcome and number of favourable prognostic factors. Survival of patients in Group 3/4 are shown as solid lines. Solid black line and solid grey line show the survival of patients with no residual tumour and residual tumour at SCS, respectively. Survival of patients in Group 1/2 are shown as dotted lines. Dotted black line and dotted grey line show the survival of patients with no residual tumour and any residual tumour at SCS, respectively.

DISCUSSION

We achieved surgical removal of all visible tumours in 59.1% of patients at the time of SCS. Residual tumours <1 or $\geqslant 1$ cm in diameter were present in 25.0 and 15.9%, respectively. In line with previous reports, removal of all visible tumours at SCS contributed to long-term survival (Figure 2). The rate of complete resection (59.1%) in our series was a little lower than the rates reported by Eisenkop *et al* (2000), Landoni *et al* (1998) and Cormio *et al* (1999). However, in Landoni's study, the subjects were restricted to those patients who were sensitive to first-line chemotherapy and chemotherapy before SCS. Cormio *et al* also restricted the subjects to patients with apparently isolated and resectable tumours and without ascites. Our criteria for patient selection were similar to those of Eisenkop *et al*, and their subjects were patients with DFI >6 months and without liver metastases. They achieved an 82% complete resection rate by using argon beam laser to remove disseminated cancer foci and reported 44 months in median survival and approximately 35% in 5-year survival in the completely resected cases. In our experience, median survival and 5-year survival in completely resected cases were 52 months and 47.6%, respectively, being much better than previous reports. Our rate of optimal cytoreduction, 84.1% (if defined as residual tumour <1 cm), was similar to the rate of complete resection in Eisenkop's report. In our series, optimally resected cases had 40 months in median survival and 38.6% in 5-year survival (figure not shown), in keeping with the survival of completely resected cases in Eisenkop's study. These findings suggest that the debulking efforts performed at SCS in our cases are comparable to those of previous reports.

Univariate analyses revealed that three factors during primary treatment (peritoneal spread, aortic lymph node metastasis, FIGO stage) and five factors at recurrence (DFI, liver metastasis, number of tumours, size of maximum tumour, SCS outcome) were significantly related to overall survival after recurrence. In the multivariate analysis excluding SCS outcome, the significance of all the three factors during primary treatment disappeared. Four factors determined at recurrence, that is, DFI, presence of liver metastasis, number of tumours and size of maximum tumour, were revealed to be independent prognostic factors.

DFI is the most important prognostic factor after recurrence, as described in many previous reports. In most studies, the cutoff period of DFI was set to 12 months. Two cutoff periods were set in Eisenkop's study (Eisenkop *et al*, 2000) (12 and 36 months) and in Tay's study (Tay *et al*, 2002) (12 and 24 months), and patients were divided into three groups. Although we also analysed our patients with DFI >12 months using cutoff periods such as 24 and 36 months, there were no significant differences between patients with and without DFI >24 or 36 months (data not shown). Recently, Zang *et al* (2004) performed SCS even in patients with DFI of 3 months and reported negative influence of DFI on overall survival. However, their follow-up period was only 16 months. This might be too short to detect a statistical difference.

Size of maximum tumour was also identified by Eisenkop *et al* (2000) as an independent prognostic factor. Eisenkop *et al* used 10 cm as the cutoff size, whereas we used 6 cm. The difference may be due to our earlier detection of recurrent tumours by using ultrasonography or CT scan within a 3-month interval. In our cases, there were only two patients in whom maximum tumour size exceeded 10 cm in diameter. At all events, tumour size seems to be an important factor reflecting biological aggressiveness of recurrent tumours.

The number of recurrent tumours has not been previously highlighted as a prognostic determinant. One reason is that some studies restricted the subjects for SCS to patients with isolated tumours or a solitary tumour (Cormio *et al*, 1999; Munkarah *et al*, 2001; Scarabelli *et al*, 2001). Another possible reason is that Eisenkop *et al* (2000) and Tay *et al* (2002) did not analyse the

number of recurrent tumours as a factor influencing survival, although they pointed out that this factor may influence SCS outcome. In concordance with our results, Zang *et al* (2004) reported that the number of recurrent tumours influenced both overall survival and SCS outcome.

The current study revealed that liver metastasis is another important prognostic determinant. Vaccarello *et al* (1995) examined the relationship between site of recurrence and survival, and reported that liver metastasis had a negative influence on survival. In most studies, patients with liver metastasis were excluded from subjects for SCS. In our series, two patients with solitary liver metastasis were included: one patient underwent hepatic resection and the other patient did not undergo hepatic resection because of the presence of unresectable metastatic portal lymph nodes. They did not achieve good survival (20 and 14 months, respectively).

From the results of the multivariate analysis, we propose the following criteria for patient selection for SCS. Patients with recurrent ovarian cancer should be considered as ideal candidates for SCS when they have three or all of the following four factors at recurrence: (1) DFI >12 months, (2) no liver metastasis, (3) a solitary tumour and (4) tumour size <6 cm. Considering our original patient selection, we should propose exclusion criteria including (1) age at recurrence $\geqslant 75$ years, (2) PS 3 or 4 just before SCS and (3) progressive disease during presurgical chemotherapy, if undertaken. Although we used intraoperative findings for the number and size of tumours, size of maximum tumour was consistent between intraoperative findings and imaging in available cases. Therefore, we can accurately evaluate all these factors, except the number of tumours, before SCS. As for the number of tumours, ultrasonography or CT scan before SCS cannot always identify multiple peritoneal disseminated tumours. When the patient meets the criteria for SCS preoperatively, it is recommended to decide whether SCS should be accomplished after reconfirming the criteria at the time of laparotomy.

In the previous studies, several prognostic factors were shown to have significant correlation with overall survival of the patients. However, these factors were obtained from SCS in selected patients in most of the previous studies. In addition, how to use several significant prognostic factors to select good candidates for SCS was not fully analysed. To our knowledge, generally accepted or recommended selection criteria are 'patients with longer DFI' (Bristow *et al*, 1996; Roberts, 1996; Rose, 2000; Sijmons and Heintz, 2000). Thus, it was sometimes difficult to decide whether or not SCS should be performed in patients who have some favourable factors and a few unfavourable factors. We believe that our selection criteria for SCS should be helpful in deciding whether SCS should be performed.

In conclusion, our data suggest that patients with three or all four of the above-mentioned favourable factors are ideal candidates for SCS, and that the final decision should be made at laparotomy in borderline cases. It seems that SCS has a large impact on survival of patients with recurrent ovarian cancer when the patients are selected by the new criteria (47 months in median survival and 45.9% in 5-year survival). However, these patients were likely to have good sensitivity to chemotherapy, because they had DFI >6 months. In a recent trial of recurrent ovarian cancer with DFI >6 months, patients who received platinum-based chemotherapy with or without paclitaxel had a favourable prognosis: 29 and 24 months in median survival and around 20% in 5-year survival, respectively (Parmar *et al*, 2003). Although patients undergoing SCS using the new criteria of patient selection seem to have much better survival than patients receiving chemotherapy alone, our study was retrospective and noncomparative, and our data were based on a relatively small number of strictly selected patients. To provide solid evidence for the therapeutic benefit of SCS and to find better selection criteria for the surgery, further studies including randomised controlled studies are required.

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CLINICAL INVESTIGATION **Cervix**

EARLY DETERMINATION OF UTERINE CERVICAL SQUAMOUS CELL CARCINOMA RADIORESPONSE IDENTIFIES HIGH- AND LOW-RESPONSE TUMORS

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Purpose: To investigate whether early-assessed radioresponse of tumors corresponds with late-assessed radioresponse, which is associated with local disease control in radiotherapy (RT) for cervical cancer.
Methods and Materials: This prospective study included 12 patients with cervical squamous cell carcinoma treated by RT with or without concurrent cisplatin. Tumor volume was estimated by scheduled magnetic resonance imaging before (preRT), 3 to 4 weeks after (early assessment), and 6 to 7 weeks after (late assessment) RT initiation. Radioresponse was assessed with tumor shrinkage curves based on these volumes. Radioresponse for each tumor was calculated as the slope (day^{-1}) of the shrinkage curve by fitting to an exponential equation.
Results: Early-assessed radioresponse ranged from 0.001 to 0.106 day^{-1} (median, 0.021 day^{-1}) and late-assessed radioresponse from 0.009 to 0.091 day^{-1} (median, 0.021 day^{-1}), with no significant difference between them (p = 0.1191). The early-assessed radioresponse correlated with the late-assessed radioresponse (R^2 = 0.714, p = 0.0005).
Conclusions: Correspondence between early- and late-assessed radioresponse in a series of tumors showing a wide range of radioresponse was not particularly close overall. However, early assessment of radioresponsiveness did seem to be useful for characterizing those tumors with high or low radioresponsiveness. © **2006 Elsevier Inc.**

Radiosensitivity, Intracavitary radiotherapy, Minimum target dose, Chemoradiotherapy.

INTRODUCTION

In radiotherapy (RT) for uterine cervical cancer, significant predictors of local disease control include not only clinical stage but also pretreatment tumor size and tumor radioresponse (1–5). Of the latter two, radioresponse is of greater practical importance because whereas pretreatment tumor size is deterministic, radioresponse is subject to modification, for example by concurrent chemotherapy. The degree of tumor shrinkage is commonly used as an index of radioresponse (6, 7)—for example, complete response (disappearance, 100% decrease in volume), partial response (≥65% decrease), and stable disease (<65% decrease). A complete response at the end of RT, which is assessed by subjective pelvic examination, is usually associated with local disease control (3–5). It would therefore be valuable to be able to predict early in the course of RT whether a tumor is to achieve a complete response; if not, intensification of treatment or the use of additional treatment could be considered earlier than otherwise possible. However, because the degree of tumor shrinkage is categorical and independent of time, it is not suitable as an index for the early estimation of radioresponse. In contrast, the speed of tumor shrinkage, another expression of radioresponse, is continuous and a function of time and pretreatment tumor size and should therefore serve as a useful index for prediction of posttreatment size.

Here, we prospectively investigated whether the speed of tumor shrinkage as assessed in the early phase of RT corresponds with that assessed in the late phase of RT, under conditions of standard clinical practice for concurrent chemoradiotherapy as proposed by the U.S. National Cancer Institute (8).

METHODS AND MATERIALS

Patients

The study group consisted of 12 patients with cervical squamous cell carcinoma selected from 19 consecutive cervical squamous cell carcinoma patients treated primarily by RT with or without concurrent cisplatin chemotherapy between December 2003 and

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December 2004. Following normal clinical practice, patients were scheduled to undergo magnetic resonance imaging (MRI) of the pelvis in three phases of RT, namely before and at 3 to 4 weeks (early phase) and 6 to 7 weeks (late phase) after the start of RT. The accuracy and clarity of MRI in demonstrating cervical tumors has been confirmed (9, 10). Seven patients were excluded from the study because not all MR images were available or because the images did not clearly identify the tumor. Clinical disease stages according to the International Federation of Gynecology and Obstetrics staging system were IB1 (n = 1), IIB (n = 1), and IIIB (n = 10). Patients ranged in age from 37 to 81 years (median, 51 years).

Treatment

Radiotherapy consisted of external and intracavitary RT. External RT was performed with a 10-MV X-ray in 1.8-Gy fractions at 5 fractions per week. Clinical target volume was the pelvis (n = 5) or the pelvis plus para-aortic nodes (n = 7), with para-aortic nodes treated prophylactically. A conformal box-field technique was used for all but 1 patient, in whom anterior–posterior opposing portals were used. A central block was placed in the pelvic RT field for the start of intracavitary RT after a total dose of 45.0 Gy (stage IIIB) or 36.0 Gy (stages IB1 and IIB) was reached. Total dose to the pelvis ranged from 50.4 to 66.6 Gy (median, 54.0 Gy), including boost doses to parametrial induration or lymphadenopathy, and total dose to the para-aortic nodes was 45.0 Gy. Intracavitary RT was performed with a high-dose-rate remote afterloading system. The prescribed dosage to reference point A was 6.0 Gy per insertion at three (n = 10) or four (n = 2) weekly insertions per patient. One patient underwent an interstitial implant after three intracavitary insertions. Thus, overall RT treatment duration ranged from 42 to 63 days (n = 11; median, 50 days) and was 70 days for the patient treated by interstitial implant.

Ten patients were treated by concurrent chemotherapy with cisplatin, and 2 (both aged 81 years) were treated by RT alone. Cisplatin was given by single weekly i.v. administration at 35 mg/m^2 (n = 3), 30 mg/m^2 (n = 6), or 20 mg/m^2 (n = 1, aged 72 years) for 3–6 weeks, starting from the first (n = 5), second (n = 4), or third week (n = 1) of RT. Delayed chemotherapy (n = 5) was due to renal dysfunction caused by hydronephrosis, which was managed by nephrostomy.

Tumor measurement with MR images

Magnetic resonance imaging was performed with 1.5-T units. The preRT images were obtained from 1 to 26 days (median, 11 days) before RT, with early-phase images obtained from 18 to 34 days (median, 24 days) and late-phase images obtained from 36 to 59 days (median, 46 days) after the start of RT, the latter being before (n = 1) or during (n = 11) the intracavitary RT course. Tumors identified as high-intensity lesions on T2-weighted images were measured three-dimensionally by width, thickness, and length for each tumor, and tumor volume was calculated on the assumption that the tumor mass was ellipsoid. The volume of tumors that disappeared or were recognized as only a remnant was regarded as 0.01 cm^3, whereas that of those remaining as a small, high-intensity "scar" that was difficult to measure was regarded as 0.05 cm^3.

Radioresponse assessment

Estimated tumor volumes were plotted on a semilogarithmic graph, with the start of RT set as Day 0. The early-phase shrinkage curve was calculated from the preRT and early-phase volumes, the late-phase shrinkage curve from the early-phase and late-phase volumes, and the through-phase shrinkage curve from the preRT and late-phase volumes. The slope of the curve (day^{-1}) (i.e., the speed of shrinkage per day) was determined by fitting an exponential regression equation to the respective curve. Radioresponse was defined as the speed of shrinkage, with radioresponsive tumors thus characterized by steep slopes. With the equation of the through-phase shrinkage curve, the tumor volume at the end of RT (postRT volume) was duly calculated for each tumor and categorized according to the degree of shrinkage. For this, either shrinkage to ≤0.05 cm^3 or to <1% of the preRT volume was regarded as complete response, whereas shrinkage to <35% of the preRT volume and shrinkage confined to ≥35% of the preRT volume were defined as partial response and stable disease, respectively.

Statistical analysis

The early-assessed radioresponse was compared with the late-assessed and with the through-assessed radioresponse. Differences in response between phases were analyzed by the Wilcoxon signed rank test. Correlation between the early-assessed and through-assessed radioresponses was analyzed by regression analysis. Radioresponse was compared between the speed of shrinkage (through-assessed radioresponse) and the degree of shrinkage. StatView 5.0 (SAS Institute, Cary, NC) was used for all analyses. P values of <0.05 were considered statistically significant.

RESULTS

The preRT volume ranged from 2.3 to 301.6 cm^3 (median, 95.5 cm^3). Complete response was observed in the early phase in one tumor and in the late phase in two (Fig. 1). Radioresponse ranged from 0.001 to 0.106 day^{-1} (median, 0.021 day^{-1}) in the early phase, from 0.013 to 0.121 day^{-1} (median, 0.025 day^{-1}) in the late phase, and from 0.009 to 0.091 day^{-1} (median, 0.021 day^{-1}) in the through phase. Radioresponse did not differ significantly between the early and late phases or between the early and through phases (p = 0.1361 for both). When the tumor that achieved a complete response in the early phase was excluded, however, the difference in response between the early and late

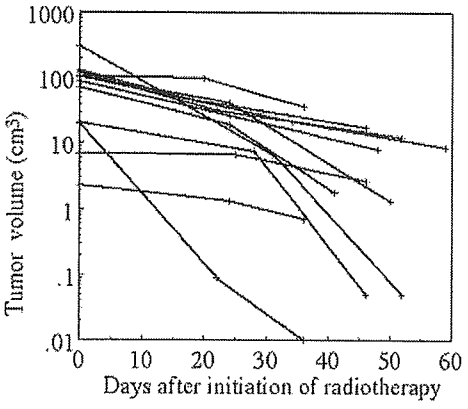

Fig. 1. Tumor shrinkage curves composed of three-phase volumes of preradiotherapy, early phase (3 to 4 weeks), and late phase (6 to 7 weeks) (n = 12).

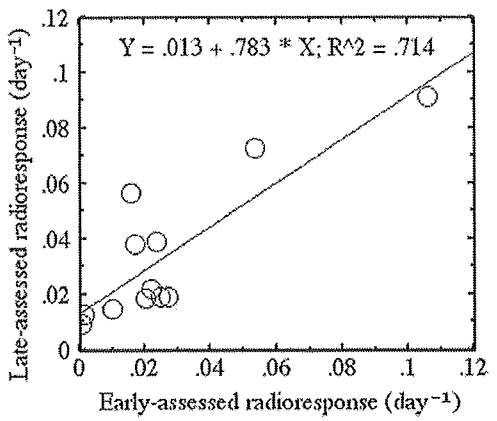

Fig. 2. Correlation between early-assessed and late-assessed radioresponse (n = 12, p = 0.0005).

phases approached significance, with radioresponse greater in the late (range, 0.013–0.121 day^{-1}; median, 0.022 day^{-1}) than in the early phase (range, 0.001–0.054 day^{-1}; median, 0.021 day^{-1}) (n = 11, p = 0.0505).

The early-assessed radioresponse correlated with the late-assessed radioresponse (Fig. 2; R^2 = 0.714, p = 0.0005). This correlation remained significant even when the tumor that achieved a near-complete response was excluded (n = 11, R^2 = 0.496, p = 0.0155).

The postRT volume ranged from 0.01 to 21.95 cm^3 (median, 0.41 cm^3) and was ≤0.05 cm^3 in three tumors. The postRT volume as a percentage ranged from 0 to 17.8% (median, 4.5%) of the preRT volume. Response category was complete response for five tumors and partial response for the remaining seven (Fig. 3). None was categorized as stable disease.

DISCUSSION

Characterization of radioresponse is particularly important for large tumors, from the standpoint of not only radiosensitivity but also dose delivery by intracavitary RT, which is characterized by steep dose fall-off within the tumor. Given that radioresponse normally implies generic radiosensitivity of tumor cells, tumors with low radioresponsiveness require larger doses for local disease control than those with high radioresponsiveness. Nevertheless, large tumors with low radioresponsiveness receive smaller target doses at the tumor periphery (minimum target doses) by intracavitary RT than large tumors with high radioresponsiveness, because the latter undergo significant shrinkage subsequent to the preceding external RT (11). Compared with large tumors, small tumors receive substantially higher minimum target doses irrespective of tumor shrinkage induced by external RT, and these high doses are considered to effectively overcome any radioresistance.

Tumors were categorized by the degree of shrinkage into either complete response or partial response only. Whereas complete response is characterized by shrinkage within a very narrow range (99–100% decrease), partial response is characterized by a wide range of shrinkage (65%–99% decrease) and is therefore not suitable for differentiating tumors at the respective ends of this range. In contrast, the speed of shrinkage is shown as a variable specific to the individual tumor and is therefore useful for differentiating partial response tumors by calculation, if the shrinkage is fitted well by a regression equation.

Our results showed that the early-assessed radioresponse corresponded with the late-assessed radioresponse, although not particularly closely. In contrast, Gong *et al.* (12), who used frequent, rigidly scheduled MRI (four to eight times per patient) and sophisticated tumor measurement methods, reported that the radioresponse of cervical tumors is exponential. Several possible reasons for this apparent discrepancy can be suggested.

First, Gong *et al.* investigated radioresponse during simple treatment with external RT alone, whereas our study involved complex treatment. Second, most of our tumors were treated by concurrent chemotherapy that was nevertheless not always simultaneous with the start of RT and by intracavitary RT that was performed in the late phase. The impact of our treatment might therefore have differed between phases, or even by week. In fact, we previously showed that the use of concurrent chemoradiotherapy tends to increase radioresponse over that achieved with RT alone (13). Further, radioresponse might have been underestimated in our three tumors that achieved a complete response because the response might have occurred before the time of observation. On these bases, we suggest that the lack of a clear exponential radioresponse in the present study was likely due to the complex treatment given, in addition to differences in the accuracy and frequency of tumor measurement.

Although exact correspondence was not obtained, our response assessment, conducted under conditions of stan-

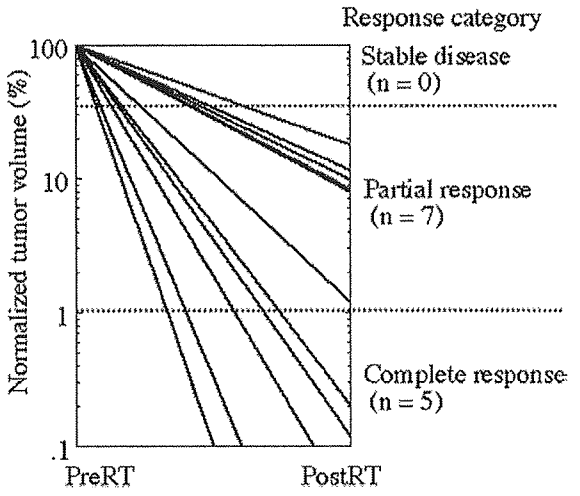

Fig. 3. Comparison of calculated radioresponse at the end of radiotherapy (RT) between the speed of shrinkage (curves) and the degree of shrinkage (response category). The postRT volume was calculated with the regression equation for each tumor at the end of RT for each individual (42–63 days from the start of RT).

dard clinical practice, is considered effective in the differentiation of highly (e.g., >0.05 day^{-1}) and poorly radioresponsive (e.g., <0.02 day^{-1}) tumors, which here represented the upper and lower quartiles of tumors by response, from those moderately radioresponsive, which made up the middle half of tumors. This is because the wide radioresponse seen facilitates the recognition of tumors at the respective ends of radioresponsiveness. Moreover, this finding is consistent between our results and those of Gong *et al.*: radioresponse range from 0.001 to 0.106 day^{-1} (early phase, 106-fold variation) and from 0.009 to 0.091 day^{-1} (through phase, 10-fold variation) in the present study and from 0.007 to 0.182 day^{-1} (26-fold variation, by planimetry) in Gong *et al.* (12).

The U.S. National Cancer Institute has recommended the concurrent use of RT and chemotherapy with cisplatin or cisplatin plus fluorouracil (as radiosensitizers) in place of the conventional use of RT alone to improve survival in patients with locally advanced cervical cancer (8), and the efficacy of this treatment has been confirmed by systematic review and meta-analysis (14). However, this recommendation is based on the assumption that the radioresponse of tumors is unknown. Early knowledge of the radioresponsiveness of tumors during treatment would allow the individualization of treatment. Given that a substantial proportion of patients have been cured by conventional RT treatment alone, those with highly radioresponsive tumors, so-called radiosensitive tumors, might not necessarily require concurrent chemotherapy. Conversely, patients with poorly radioresponsive tumors, so-called radioresistant tumors, might benefit from the intensification of treatment, such as the planned use of interstitial implants and the incorporation of a potent new radiosensitizer (gemcitabine) into concurrent chemotherapy (15).

In conclusion, the early-assessed radioresponse of uterine cervical squamous cell carcinoma corresponded with the late-assessed radioresponse, albeit not particularly strongly. Although it would be premature to incorporate these findings directly into local disease control, early determination might nevertheless be useful for identifying tumors at either extremity of the wide radioresponse range seen here.

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Special article

Current status and future prospects of chemotherapy for metastatic gastric cancer: a review

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Abstract

Although many randomized trials of chemotherapy for metastatic gastric cancer have been reported during the past two decades, no standard regimens worldwide have been established yet. Reference arms vary depending on the region and cultural differences. To date, a combination of 5-fluorouracil (5-FU) and cisplatin is most widely used. However, no confirmation of survival advantage over single-agent 5-FU in a randomized trial has been proved yet, and there remain limitations of efficacy results in older-generation regimens. Recently developed new agents such as irinotecan, taxanes (paclitaxel and docetaxel), and new oral fluorouracil (S-1 and capecitabine) provided more promising results: a response rate over 50% and median survival time (MST) over 10 months in their preliminary combination studies. These newer combination regimens are now being investigated in various randomized phase III studies, which will clarify whether the newer-generation regimens provide survival advantage over older-generation regimens. The MST of the new standard should exceed 11 months to be considered a definite improvement, and overall survival seems to be a more desirable primary end point than progression-free survival in a randomized trial. Molecular targeting agents are another concern to improve the treatment outcomes of this disease and are now under investigation in combination with conventional cytotoxic agents. Both clinical and biological research will be more important in future studies.

Key words Gastric cancer · Chemotherapy · Treatment · Molecular targeting agent

Introduction

Unresectable advanced or recurrent gastric cancer still has a poor prognosis, with a median survival of less than 9 months. Randomized trials demonstrated that 5-fluorouracil (5-FU)-based regimens provide superior survival and quality of life in patients with advanced gastric cancer when compared with the best supportive care [1–3]. However, this survival advantage appears to be marginal, and no standard regimens worldwide have been established yet.

Recently developed new agents, such as irinotecan, S-1, capecitabine, docetaxel, paclitaxel, and oxaliplatin may have potentials that will break through this status. Newer-generation regimens with these agents are now being investigated in randomized trials throughout the world. Molecular targeting agents are another new topic in the field of chemotherapy and are also under development for gastric cancer treatment. This review focuses on the results of newer-generation regimens with a brief summary of older-generation regimens.

Overview of the older-generation regimens

Results from randomized controlled trials (Table 1)

During the past two decades, various randomized trials have been carried out for metastatic gastric cancer. Despite the numerous efforts, there is no accepted global standard regimen at present, and reference regimens differ according to cultural and regional differences. In Europe, a combination of fluorouracil, doxorubicin, and high-dose methotrexate (FAMTX) used to be a standard regimen based on the European Organization for Research and Treatment of Cancer (EORTC) trials [4]. However, this regimen failed to demonstrate any superiority over other combination regimens (5-FU plus cisplatin or etoposide plus 5-FU/leucovorin) in the subsequent EORTC randomized study [5]. Another randomized study in the United Kingdom revealed superiority of a combination of epirubicin, cisplatin, and 5-FU (ECF) over FAMTX in terms of survival [6], while survival results of these

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Table 1. Results of randomized trials using older-generation regimens

Study (ref #)	Treatment	No. of patients	Response rate (%)	Median survival (months)	*P* value
Wils 1991 [4]	5FU+ADM+MMC	103	7	6.7	0.004
	5FU+ADM+MTX	105	33	9.6	
Kim 1993 [8]	5FU	94	26	6.9	ns
	5FU+ADM+MMC	98	25	6.6	
	5FU+CDDP	103	51	8.5	
Webb 1999 [6]	5FU+ADM+MTX	130	21	5.7	0.0009
	Epirubicin+CDDP+5FU	126	45	8.9	
Vanhoefer 2000 [5]	5FU+CDDP	134	20	7.2	ns
	Etoposide+LV/5FU	132	9	7.2	
	5FU+ADM+MTX	133	12	6.7	
Ohtsu 2003 [9]	5FU	106	11	7.1	ns
	5FU+CDDP	104	34	7.3	
	UFT+MMC	70	9	6.0	

ns, not significant; 5FU, 5-fluorouracil; ADM, doxorubicin; MMC, mitomycin C; MTX, methotrexate; CDDP, cisplatin; LV, leucovorin; UFT, uracil and tegafur

Table 2. Treatment results of new agents: monotherapy

Agent	No. of patients[a]	Response rate	MST (M)
CPT-11	76 (20)	18% (25%)	NS (NS)
S-1	101 (101)	45% (45%)	8.3 (8.3)
Capecitabine	44 (44)	34% (34%)	9.5 (9.5)
Docetaxel	40 (40)	18% (18%)	11.0 (11.0)
Paclitaxel	60 (28)	23% (21%)	11.5 (11.4)

MST, median survival time; NS, not stated; CPT-11, irinotecan
Parentheses indicate results in the chemonaive patients

studies were limited with a median survival time (MST) ranging from 6 to 8 months and no confirmation of superiority of ECF over two-drug combinations such as cisplatin (CDDP) plus 5-FU (CF). Other trials including using 5-FU alone as a reference arm and comparing it with FU-based combination regimens have been reported from the United States, Korea, and Japan [7–9]. All three trials showed similar results: combination regimens failed to demonstrate survival prolongations as compared with 5-FU alone, while response rates and progression-free survival in the CF arm were superior to single-agent 5-FU.

Based on the results of these randomized trials, CF could be a reasonable reference arm. However, even this regimen has not shown superiority to 5-FU alone in terms of overall survival, and there still are limitations on efficacy results in older-generation regimens: the response rates ranged from 10% to 35%, and the MSTs from 6 to 8 months with around 10% in 2-year survival. To overcome these limitations, new active agents were essential.

Current status of new-generation regimens

Single-agent studies

Recently, new-generation agents such as irinotecan, S-1, capecitabine, docetaxel, paclitaxel, and oxaliplatin have been developed and investigated for gastric cancer with promising activities [10–15]. Results of single-agent studies are summarized in Table 2. Of the five agents, S-1 achieved the highest response rate, 45%; and the other agents also showed moderate activity, with response rates of 18% to 34%. These active agents are now being investigated in combination with other agents.

Combination studies (Tables 3, 4)

Irinotecan and its combinations

Irinotecan is an inhibitor of DNA-topoisomerase I, which is a crucial enzyme involved in DNA replication and transcription. At first this agent was investigated in combination with CDDP in Japan [16,17]. A phase II study of this combination (irinotecan at 70 mg/m^2, day 1 and 15, and CDDP at 80 mg/m^2, day1 every 4 weeks)

Table 3. Treatment results of newer-generation regimens: two-drug combinations

Regimen	Phase	*n*	Response rate	MST (M)	Reference (year)
Irinotecan+CDDP	II	29	59%	10.8	17 (1999)
Irinotecan+5-FU/LV	II	59	42%	10.7	35 (2004)
S-1+CDDP	I/II	25	76%	12.5	22 (2003)
S-1+irinotecan	I/II	24	50%	NS	23 (2002)
Capecitabine+CDDP	II	42	55%	10.1	27 (2002)
Capecitabine+docetaxel	II	47	40%	12	28 (2004)
Docetaxel+CDDP	II	48	56%	9	31 (2000)
Oxaliplatin+5-FU/LV	II	41	43%	9.6	33 (2004)

NS, not stated

Table 4. Treatment results of newer-generation regimens: three-drug combinations

Regimen	Phase	*n*	Response rate	MST (M)	Reference (year)
Paclitaxel+CDDP+5-FU	II	41	55%	6	30 (1999)
Docetaxel+capecitabine+CDDP	II	40	68%	17	35 (2004)
Docetaxel+CDDP+5FU	III	111	39%	10.2	34 (2003)

achieved a high response rate of 48% with an MST of 9 months in all patients, and of 59% with an MST of 11 months in chemonaive patients. Toxicities were substantial, the major ones being neutropenia and diarrhea: grade 4 neutropenia was observed in 57% of patients and grade 3 or 4 diarrhea in 20%. This combination has been modified to a weekly schedule in order to reduce toxicity and has been followed in Western countries. Both of the phase II studies in the United States showed similar activity, with response rates of 58% and 57% [18,19]. This combination is now being investigated in a randomized phase III trial in Japan.

Another combination was conducted with mitomycin C; the phase I/II study of this combination revealed similar efficacy results and less toxicity than an irinotecan/CDDP regimen [20]. This regimen was then evaluated in the phase II study as a second-line setting after the failure of FU-based regimens [21]. Of the 45 patients registered, 13 achieved partial response, with a response rate of 29%. Median progression-free survival was 4 months. Toxicities were moderate: grade 4 neutropenia was observed in 29% of patients and grade 3 anorexia in 24%. This study concluded that this regimen could be a treatment option in patients resistant to an FU-based regimen.

Oral fluoropyrimidines and their combinations

S-1 is a new oral fluoropyrimidine consisting of three components: tegafur, which is a prodrug of 5-FU; 5-chloro-2,4-dihydroxypyridine (CDHP), which competes with dihydropyrimidine dehydrogenase; and oxonic acid, which suppresses the gastrointestinal toxicity of tegafur. Various attempts in combination with other agents such as CDDP, irinotecan, and taxanes have been conducted, particularly in Japan. At first, this agent was combined with CDDP. This combination phase I/II study was scheduled as S-1 40 mg/m^2 twice daily for 21 consecutive days and 2-h infusion of CDDP at 60–70 mg/m^2 on day 8, which was repeated every 5 weeks [22]. This study revealed an excellent response rate of 76% with an MST of 12.6 months. Toxicities were moderate but easily manageable: grade 3 or 4 hematological and nonhematological toxicities were 15.8% and 26.3%, respectively. Another combination, S-1+CPT-11, is also promising. A phase I/II study of this combination revealed similar response rates of around 50% with an MST of 14 months [23].

In spite of the promising results in Japan, the development of this agent in Western countries has been interrupted due to severe diarrhea as a side effect. The first European single-agent phase II study had to be decreased from 40 to 35 mg/m^2 owing to significant diarrhea [24]. These differences might be caused by higher susceptibility to diarrhea or lower absorption of oxonic acid in Western populations [25]. However, this agent is now being retested using lower doses in the United States. Ajani et al. reported a phase I study of S-1 in combination with CDDP [26]. The predominant dose-limiting toxicities were fatigue, diarrhea, and mucositis. Although the maximum tolerated dose of the study (S-1 at 25 mg b.i.d for 3 weeks and CDDP at 75 mg/m^2 every 4 weeks) was different from that of the Japanese study, the preliminary results were promising and a phase II study is now underway in the United States.

The activity of capecitabine for gastric cancer has also been reported, particularly from Korea. This agent

Table 5. Ongoing large-scale randomized phase III trials for metastatic gastric cancer

Regimen	Target accrual (patients)
Western trials	
CDDP+5-FU vs. docetaxel+CDDP+5-FU	462
CDDP+5-FU vs. irinotecan+5-FU/LV	337
Epirubicin+CDDP+5-FU vs. epirubicin+oxaliplatin+5-FU vs. Epirubicin+CDDP+capecitabine vs. epirubicin+oxaliplatin+capecitabine	600
Asian trials	
CDDP+5-FU vs. capecitabine+CDDP	300
Japanese trials	
5-FU vs. irinotecan+CDDP vs. S-1	690
S-1 vs. S-1+CDDP	300
S-1 vs. S-1+irinotecan	300

was first investigated in combination with CDDP (capecitabine at 1250 mg/m², days 1–14, and CDDP at 60 mg/m², day 1 every 3 weeks), showing a response rate of 55% with an MST of 12 months in a phase II study [27]. Similar promising results were observed with a combination of capecitabine and docetaxel [28]. Kang et al. reported three drug combinations consisting of capecitabine at 1125 mg/m², days 1–14, docetaxel at 60 mg/m², day 1, and CDDP at 60 mg/m², day 1, repeated every 3 weeks, which resulted in a high response rate of 68% (27/40) with a long MST of 17 months [29]. These results warrant further investigations of these capecitabine-based combinations and should be evaluated in large-scale randomized trials.

Taxanes and their combinations

The taxanes docetaxel and paclitaxel inhibit microtubule depolymerization and have moderate activity against gastric cancer, with a response rate of around 20% in single-agent studies. Paclitaxel was combined with a CF regimen in the Korean phase II study [30]. Although this three-drug combination achieved a high response rate of 51% (21/41), an MST of 6 months seemed disappointing. The Swiss Group for Clinical Cancer Research has reported a phase II study of docetaxel 85 mg/m² with CDDP 75 mg/m² administered once every 3 weeks for advanced gastric cancer, achieving a response rate of 52%, median time to progression of 6.6 months, and an MST of 9 months [31]. This combination was then followed by three-drug combinations adding 5-FU and has been investigated in the randomized trial described later.

Oxaliplatin and its combinations

Oxaliplatin is an alkylating agent inhibiting DNA replication by forming adducts between two adjacent guanines or guanine and adenine molecules. With the success of the combination of oxaliplatin and 5-FU/leucovorin (LV) for colorectal cancers, this combination was tested for gastric cancer. Louvet et al. reported a phase II study of oxaliplatin in combination with infusional 5-FU/LV (FOLFOX6) for advanced or metastatic gastric cancer, which resulted in a response rate of 45% and an MST of 8.6 months [32]. However, FOLFOX6 caused significant toxicity including myelosuppression and peripheral neuropathy. Subsequently the regimen was revised with a reduced dose of oxaliplatin and without bolus infusion of 5-FU. The revised phase II revealed a similar response rate and MST of 9.6 months, with less toxicity than those in the previous study [33]. The authors concluded that the modified FOLFOX6 regimen provided efficacy results comparable with other combination regimens with significantly less toxicity.

Randomized controlled trials including newer-generation regimens

As mentioned above, various combination regimens including new agents showed promising results in the phase II studies, with response rates of around or above 50%. Most of the new-generation regimens are now being evaluated to determine whether they would provide significant survival prolongations as compared with older-generation regimens (Table 5). Recently, an international randomized controlled trial (V-325) comparing a docetaxel-based regimen with the reference regimen of CF was reported following an interim analysis [34]. The phase II randomized portion of the study revealed an overall response rate of 28% with docetaxel/CDDP, and of 43% with docetaxel/CDDP/5-FU (DCF). Subsequently the DCF regimen was chosen as the experimental arm for the phase III stage. The doses and schedule of the DCF arm were: docetaxel 75 mg/m² on day 1, CDDP 75 mg/m² on day 1, and 5-FU 750 mg/m² per day as continuous infusion on days 1–5, repeated every 3 weeks. The dose and schedule of the CF arm were CDDP 100 mg/m² day 1 and 5-FU 1000 mg/m² per day as continuous infusion on days 1–5, administered every 4 weeks. At the interim analysis on

232 patients, time to progression was superior (P = 0.0008) for DCF (5.2 months vs 3.7 months for CF). The MST was also longer for patients receiving DCF (10.2 months) than for those receiving CF (8.5 months). Neutropenic fever, infections, diarrhea, and mucositis were also higher from DCF than from CF. To date, however, the interpretation of the V-325 study results appears to be controversial. Although this study confirmed the superiority of DCF over CF in terms of efficacy, the MST of the DCF arm was 10.2 months, which did not seem a marked improvement. The latest combination studies, as listed in Tables 3 and 4, yielded 12 months or longer MST, although patient numbers were low. Additionally, toxicity of DCF was significant, with grade 3/4 neutropenia of 84%. The decision of whether the superiority of DCF can be accepted should wait until publication of final results. Another international randomized phase II/III study (V306), which compared irinotecan/CDDP with irinotecan plus infusional 5-FU/leucovorin in the phase II portion is now under investigation, mostly in European countries [35]. In that study, 200 mg/m^2 of irinotecan and 60 mg/m^2 of CDDP were administered every 3 weeks, compared with 80 mg/m^2 of irinotecan, 500 mg/m^2 of folinic acid (leucovorin, LV), and 2000 mg/m^2 of 5-FU as a 24-h infusion per week for 6 weeks followed by 1 week of rest. The overall response rates and MSTs of irinotecan/CDDP and irinotecan/5-FU/LV were 32% and 42% and 6.9 and 10.7 months, respectively. Toxicity results also revealed more favorable profiles in irinotecan/5-FU/LV than in irinotecan/CDDP; therefore, the former regimen has been chosen as the experimental arm for the phase III portion in comparison with the control arm of CF. Superiority of the irinotecan/5-FU/LV has also been observed in a French randomized phase II study comparing 5-FU/LV with CDDP/5-FU/LV and with irinotecan/5-FU/LV [36]. These two randomized phase II studies suggest that irinotecan/5-FU/LV is the most promising combination regimen; however, confirmation by a phase III study is necessary. In Europe, there is another ongoing study with oxaliplatin used in combination with epirubicin and capecitabine. Patients are randomly assigned to one of the four regimens: ECF (epirubicin/CDDP/5-FU), EOF (epirubicin/oxaliplatin/5-FU), ECX (epirubicin/CDDP/capecitabine), and EOX (epirubicin/oxaliplatin/capecitabine). The preliminary results available in 2003 showed response rates of 31%, 33%, 35%, and 52% for ECF, EOF, ECX, and EOX, respectively [37]. Complete results will be expected in the near future. The fourth trial is now underway in Asian countries, mostly in Korea, in a study comparing 5-FU/CDDP with capecitabine/CDDP.

In the meantime, many randomized trials consisting of an S-1 based regimen are now being evaluated in Japan. Based on the results of JCOG9205 [9], the JCOG considered single-agent 5-FU as the reference arm and has initiated three-arm randomizations (JCOG9912) comparing 5-FU alone with a combination of irinotecan/CDDP and with S-1 alone. This study requires a sample size of 690 and the accrual will be completed at the end of 2005. The second study is a postmarketing randomized trial comparing S-1 alone with S-1+CDDP (sponsored by the Taiho Pharmaceutical Company), with a sample size of 300. The accrual to this study has been recently completed. The other studies are also designed to have S-1 as the reference arm: S-1 versus 5-FU/LV sponsored by Weiss, and S-1 versus S-1/irinotecan sponsored by the Yakult-Daiichi Pharmaceutical Company.

There may be significant differences between Japan and other countries in interpreting the reference arm. Most countries consider CF, some regions ECF, as the reference arm for metastatic gastric cancer. However, single-agent 5-FU is considered the reference arm in JCOG based on the results of the previous randomized trial (JCOG9205) as well as the Korean and North American trials [7–9], and S-1 monotherapy has been selected as the reference arm in the later trials in Japan. This difference was caused by the different interpretation of the trials comparing single-agent 5-FU with CF, different histories of randomized trials, and cultural differences between the regions. One might say that high response rate and long progression-free survival would provide better quality of life, but another could say that 5-FU alone would provide the same survival as CF, with less toxicity, which seemed to provide better quality of life. In addition, there might be some questions raised: whether combination regimens as front-line therapy have survival advantages over single-agent therapy; determining which is better, simultaneous or sequential combinations; and whether we have to change the primary end point to progression-free survival rather than overall survival. The above ongoing trials will answer these questions, and the MST of the new standard should exceed 11 months to be considered a definite improvement. Contrary to the recent advances in colorectal cancer, no confirmation of improving results with newer-generation regimens as compared with older-generation ones has been achieved yet. It is likely that at first we should confirm definite overall survival prolongation.

Randomized trials in patients with peritoneal metastasis

The peritoneum is the major site of metastasis from gastric cancer. However, patients with peritoneal metastasis usually are in poor general condition, with impairment of oral intake and complications such as bowel obstruction and hydronephrosis, which may prolong elimination of the agents. Patients with peritoneal dis-

semination are excluded from a phase II study because these studies usually require response evaluation as a primary end point, whereas these patients usually have no measurable lesions. Thus, a specifically targeted study should be conducted. A phase II study of sequential combination of methotrexate (MTX) plus 5-FU (JCOG9603) has been carried out in patients with malignant ascites [38]. A total of 37 patients were registered; remarkable decreases of ascites were observed in 13 patients (35%), including 4 (11%) with disappearance of ascites, while 2 (5%) patients died of treatment-related toxicity. Based on the results, a phase III study comparing 5-FU alone with MTX/5-FU (JCOG0106) in patients with peritoneal dissemination has been initiated in the JCOG and the accrual will be completed in 2005. Another randomized trial to investigate an efficacy of paclitaxel for this disease is now being conducted as a second-line therapy in JCOG.

Molecular targeting agents under investigation

Recently developed molecular targeting agents may provide a significant impact in this field, as successful results of bevacizumab and cetuximab have been observed in colorectal cancer [39,40].

Gefitinib is an orally active epidermal growth factor receptor–tyrosine kinase inhibitor that has shown single-agent action against non-small-cell lung cancer. A Japan–Europe joint phase II study was conducted to investigate the efficacy, tolerability, and pharmacokinetics of gefitinib in patients with metastatic gastric adenocarcinoma [41]. Seventy-five patients (32 Japanese, 43 non-Japanese) were randomized to receive 250 mg/day or 500 mg/day gefitinib orally. Disease control was achieved in 13 patients: 1 (250 mg/day) had a partial response and 12 had stable disease (4 at 250 mg/day, 8 at 500 mg/day), with a disease control rate of 18%. The most common drug-related adverse events were diarrhea (45.9%), rash (35.1%), and anorexia (12.2%). Drug-related grade 3/4 adverse events were experienced by 11.1% and 23.7% of patients given 250 mg/day and 500 mg/day gefitinib, respectively. Gefitinib exposure appeared to be unaffected by ethnicity or previous gastric surgery. Furthermore, there was no marked difference in plasma concentration in patients with disease control (partial response plus stable disease) versus progressive disease. In conclusion, gefitinib monotherapy was generally well tolerated but its action seemed to be limited.

Investigations of two other molecular targeting agents are now being planned. EMD72000 is a 95% humanized monocloncal antibody against EGFR that showed promising activity for colorectal adenocarcinoma in a phase I study [42]. This agent has less toxicity, particularly in allergic reaction and skin rash, than cetuximab, which is a chimeric antibody against EGFR. This agent in combination with a cytotoxic agent will be evaluated in patients with EGFR-positive gastric cancer. Another planned agent is trastuzumab, a monoclonal antibody to Her2 protein, which is widely used in patients with Her2-overexpressing breast cancer. We have evaluated the frequency of Her2 overexpression and the concordance between protein expression and gene amplification in 200 surgical and endoscopic biopsy specimens using two commercial immunohistochemical (IHC) kits (Dako Cytomation, Glostrup, Denmark) and fluorescence in situ hybridization (FISH) (VYSIS, Abbott Laboratories, Downers Grove, IL, USA) [43]. Among these 200 cases, 46 (23%) of the patients were found to exhibit Her2 protein overexpression. The following IHC scores were obtained: 0: 126 (63%); 1+: 28 (14%); 2+: 12 (6%); and 3+: 34 (17%). Gene amplification examined with FISH was observed in 54 cases (27.1%). Her2 protein overexpression was observed in 21.5% of the 200 biopsy specimens (2+: 7.5%; 3+: 14%). The concordance rate between the surgically resected materials and the biopsy specimens was 88.7%. From these background results, trastuzumab can be applied for clinical trial in patients with Her 2 overexpressed gastric cancer, and a randomized trial is now being conducted as an international study.

Although the efficacy of the molecular targeting agents is still limited, these agents are the other new hopes for improving efficacy results with less toxicity than conventional cytotoxic agents. Understanding of the biology of gastric cancer may result in better targets or cellular pathways being modified or blocked by therapeutic interventions. Additionally, improvement of the clinical trial design and molecular surrogate into clinical research will lead to the development of better treatments. Both clinical and biological research will be more important.

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