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Long-term Survival in Ovarian Cancer

Mature Data from The Netherlands Joint Study Group for Ovarian Cancer

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In two studies initiated in 1979 and 1981, 377 patients were treated for advanced epithelial ovarian cancer. In the first study patients were randomly assigned to receive Hexa-CAF (hexamethylmelamine, cyclophosphamide, methotrexate, 5-fluorouracil) or CHAP-5 (cyclophosphamide, hexamethylmelamine, doxorubicin, cisplatin for 5 days) and in the second study to receive CHAP-5 or CP (cyclophosphamide, cisplatin on 1 day). Patients who did not respond to Hexa-CAF were offered subsequent treatment that included cisplatin. Median follow-up of patients in the first study was 9.5 years and in the second study 7.7 years. At 10 years 9% of the patients initially treated with Hexa-CAF and 21% of patients assigned to CHAP-5 were alive. Among the 10-year survivors treated with Hexa-CAF, 50% had experienced progressive disease but were alive as a result of retreatment with a cisplatin regimen. The survival curves of both studies revealed that approximately 60% of the patients who reached a complete remission were alive at 5 years and 40% at 10 years. Patients with microscopic disease at second-look had a less favourable outlook: 35% survived 5 years. Not recognised at first publication of both studies was the influence of tumour grade on survival. Before 5 years of follow-up, the good prognosis of grade 1 tumours (well differentiated) could not be detected. About 50% of patients with grade 1 tumours were alive at 5 and 30% at 10 years while these survival rates were halved for the other grades. Combination chemotherapy with cisplatin can enhance survival by more than 10% at 5 and 10 years compared with the best treatment of the precisplatin era: Hexa-CAF.
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INTRODUCTION

LONG-TERM SURVIVAL data beyond 5 years of patients with advanced ovarian cancer are rare in the literature and in most reports published so far the survival curves of important subgroups are lacking. Therefore we decided to update the data from two studies performed by The Netherlands Joint Study Group for Ovarian Cancer initiated in 1979 and 1981, respectively. The first study compared a combination of hexamethylmelamine, cyclosphosphamide, methotrexate and 5-fluorouracil (Hexa-CAF) with cyclophosphamide and hexamethylmelamine alternating with doxorubicin and a 5-day course of cisplatin (CHAP-5) in 186 patients with advanced epithelial ovarian carcinoma [1]. In the second study, initiated in 1981, 191 eligible patients were enrolled and treated with either CHAP-5 or cyclophosphamide and cisplatin (CP), both administered intravenously on a single day every 3 weeks [2]. Protocol entry criteria, pretreatment staging, histology grading, the randomisation procedure, assessment and definitions of tumour response, evaluation and statistical methods were all the same in both studies. In the second study, however, 7 patients with FIGO stage II, but macroscopic residual disease after attempted debulking, were also included.

PATIENTS AND METHODS

Survival time for this analysis was defined as the period that elapsed between the start of chemotherapy and death. Time to disease progression was also counted as from start of chemotherapy. All eligible patients were included in the survival curves. Patients who died of causes other than ovarian cancer were included in the analysis. Patients who died without disease progression were dropped from the progression-free survival curves at the end of the observation period (censored). Cases withdrawn from the study not because of progression (but, for example, because of toxicity) were censored from the analysis from the day that a new therapeutic regimen was started. Survival distributions were described by the product-limit method (this allows information from censored patients to be incorporated into the estimation of the survival distribution). Patients are "censored" for the event of interest, if at the time of analysis they have not been observed to have experienced the event of interest, i.e. progression or death [3]. The generalised Wilcoxon (Breslow) statistics were used for testing the difference

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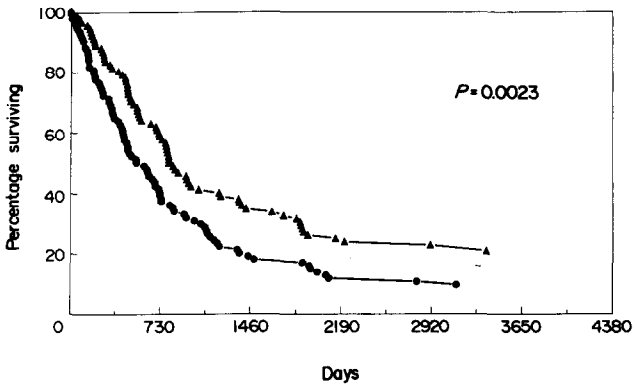

Fig. 1. Survival after treatment with Hexa-CAF or CHAP-5. ▲ = CHAP-5 (92 entered; 72 died), ● = Hexa-CAF (94; 85).

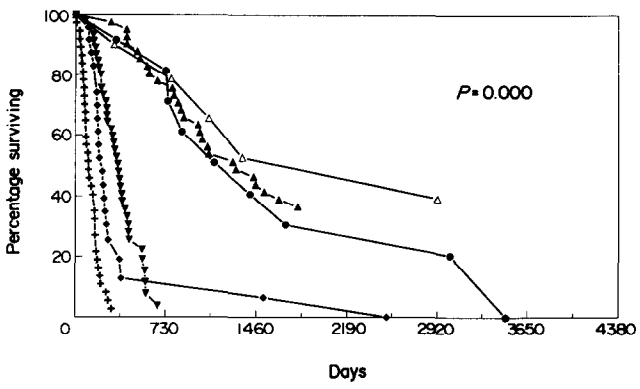

Fig. 3. Hexa-CAF and CHAP-5: progression-free survival in relation to type of response. △ = Complete remission documented by peritoneoscopy (10 entered; 5 progressed), ▲ = complete remission at laparotomy (41; 26), ● = microscopic disease (13; 9), ▼ = partial remission (46; 39), ◆ = no change (25; 20), + = progression (37; 37).

between the curves. Use was made of the BMDP statistical software package (Biomedical Computer Programs, BMDP Statistical Software, University of California, Berkeley).

RESULTS

From the first study 186 eligible patients were analysed for survival with a median follow-up of 9.5 years (range 8.5–10.5 years). As can be learned from the survival curve, 18% of the Hexa-CAF patients survived at 5 years and 9% at 10 years (Fig. 1). For patients treated with CHAP-5 these survival rates were 32 and 21%, respectively. Progression-free survival rates at 5 and 10 years were 9 and 5% for Hexa-CAF and 24 and 21% for patients allocated to CHAP-5 (Fig. 2). Progression-free survival for each response-category is presented in Fig. 3. Only 37% of the patients who reached a complete remission documented at laparotomy remained progression-free at 5 years. Although 31% of the patients with microscopic disease at second-look were free of disease at 5 years, most progressed within 10 years of follow-up.

In the second study, 191 eligible patients were included in the survival curves with a median follow-up of 7.7 years (7.1–8.5 years). 5 and 8-year survival rates for CHAP-5 were, respectively, 32% and 21%, and for CP 28% and 23% (Fig. 4). For both studies the survival of patients in relation to response and a number of prognostic factors have been computed. The data are presented in Tables 1 and 2 and Figs 5–12. No differences in survival could be detected in both studies for the histological types. The survival benefit for patients receiving CHAP-5 in the first study was significant in those with a FIGO stage III, but not in patients with a FIGO stage IV tumour (Fig. 13).

As published previously, we performed in the second study an operation in 47 patients while they were receiving chemotherapy, to remove as much tumour as possible (cytoreductive intervention surgery) [2]. Although in 63% of these cases the tumour could be removed so that only residual disease of less than 1 cm remained, this did not lead to longer survival compared to that of patients in whom the attempt was not successful. As presented in Fig. 14, this lack of difference in survival sustained with longer follow-up. The survival of patients who had successful cytoreductive surgery (leading to tumour residuals of 1 cm or less) at the staging laparotomy was significantly longer compared to patients who had successful intervention surgery (Fig. 15).

DISCUSSION

This is the first time that long-term data of two randomised studies of the Netherlands Joint Study Group for Ovarian Cancer have been presented. The data allow the final conclusions that treatment with a cisplatin-containing regimen (CHAP-5) produces superior long-term survival results compared with a

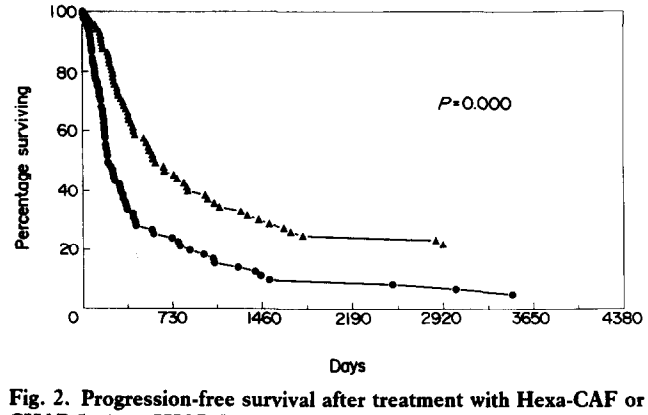

Fig. 2. Progression-free survival after treatment with Hexa-CAF or CHAP-5. ▲ = CHAP-5 (92 entered; 62 progressed), ● = Hexa-CAF (93; 77).

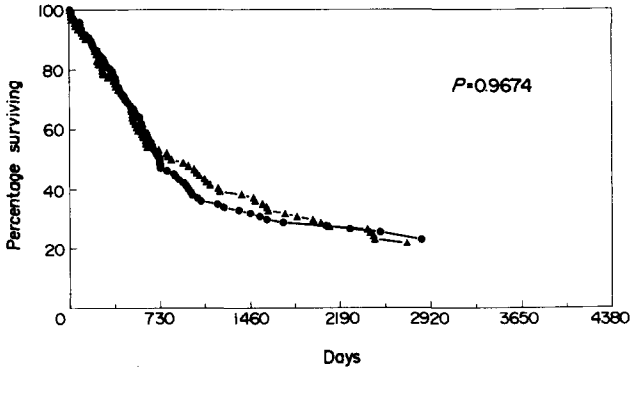

Fig. 4. Survival after treatment with CHAP-5 or CP. ▲ = CHAP-5 (94 entered; 73 died), ● = CP (97; 73).

Table 1. Survival rates of all eligible patients in 2 subsequent studies comparing Hexa-CAF with CHAP-5 (first study) and CHAP-5 with CP (second study)

	Survival rates, first study		Survival rates, second study	
	5-year	10-year	5-year	8-year
All eligible patients	25	15	30	23
Response				
Complete remission	58	39	64	51
Microscopic disease	61	31	35	29
Partial remission	7	4	12	8
No change	20	12	0	0
Progression	2	0	4	4
FIGO stage				
III	30	20	34	26
IV	12	3	14	10
Residual tumour before chemotherapy*				
Microscopic	62	37	61	48
<1 cm	46	25	41	32
1–2 cm	30	17	25	25
2–5 cm	21	17	25	22
≥5 cm	13	9	18	12
Histological grade (Broders')				
1	48	33	50	41
2	24	14	26	17
3	16	11	27	21
4	28	16	39	28
Karnofsky index				
100	26	18	39	31
90	35	19	34	29
80	26	22	25	6
70	21	8	9	9
≤60	0	0	0	0

*Largest cross-sectional diameter.

Table 2. Median survival data of all eligible patients in 2 subsequent studies, comparing Hexa-CAF with CHAP-5 (first study) and CHAP-5 with CP (second study)

	Median survival (years)	
	First study	Second study
Treatment		
Hexa-CAF	1.5	
CHAP-5	2.2	
CHAP-5		2.2
CP		2.0
Response		
Complete remission at laparotomy	5.2	7.8
Microscopic disease	5.2	4.2
Partial remission	1.6	1.6
No change	1.2	0.9
Progression	0.6	0.5
FIGO stage		
III	2.4	2.6
IV	1.3	1.4
Residual tumour before chemotherapy*		
Microscopic	5.1	6.6
<1 cm	3.2	3.8
1–2 cm	1.9	1.8
2–5 cm	1.7	1.6
≥5 cm	1.7	1.5
Histological grade (Broders')		
1	3.7	5.1
2	1.9	2.6
3	1.5	2.2
4	2.2	1.3
Karnofsky index		
100	2.2	3.3
90	2.6	1.9
80	1.9	1.8
70	1.3	1.0
≤60	0.5	1.2

*Largest cross-sectional diameter.

non-cisplatin regimen (Hexa-CAF) and that the CP regimen (preferable because of the better therapeutic index in comparison with CHAP-5) produces survival results superimposable on the survival of CHAP-5 patients.

In the first study only 9% of the Hexa-CAF patients survived for 5 years without progression. This rate is similar to the 5-year overall survival rate of patients treated with an alkylating agent alone [4]. The high overall survival rate for Hexa-CAF patients at 5 year (18%) compared with progression-free survival was a result of second remissions reached with cisplatin salvage treatment. For example, salvage with cisplatin of Hexa-CAF-treated patients with microscopic disease at second-look improved the survival of this category. As a result we found the survival of patients with microscopic disease at second-look similar to the survival of patients in complete remission. Because no effective salvage could be administered for patients treated with cisplatin as initial treatment, we found in the second study a poor survival outcome in cases with microscopic disease.

From the literature it is well known that patients who relapse on alkylating treatment may benefit from cisplatin. In a randomised trial comparing melphalan with a combination of cyclophosphamide, doxorubicin and cisplatin (CAP), for example, investigators from the Princess Margaret Hospital in Toronto, Canada, found no significant difference in overall survival between the treatments, and attributed this finding to further response when melphalan patients received CAP as second-line therapy after progression [5].

The first time that we reported on our ovarian cancer studies, a Cox's proportional hazard regression model was used to find relevant prognostic variables predicting for survival. Independent variables identified included therapy, FIGO stage, size of residual tumour and the performance status as measured by Karnofsky index. At that time, with a median follow-up of 3.3 and 3.8 years, the influence of tumour grade could not be detected. But since our data have matured beyond 5 years, the good long-term outlook for patients with well differentiated tumours (grade 1 according to the Broders' classification) is obvious. Quantifying the importance of grade in relation to the other prognostic variables (at median follow-up of 6.5 and 4.8 years), it has turned out to be of similar importance to the diameter of residual disease prior to treatment [6]. Our experience is a plea to wait with the search for factors predicting survival in ovarian cancer until the data have matured for approximately 5 years.

FIGO stage is among the independent prognostic factors (by multivariate analysis) predicting for long-term survival [6]. The survival curves presented here illustrate that only a minority of

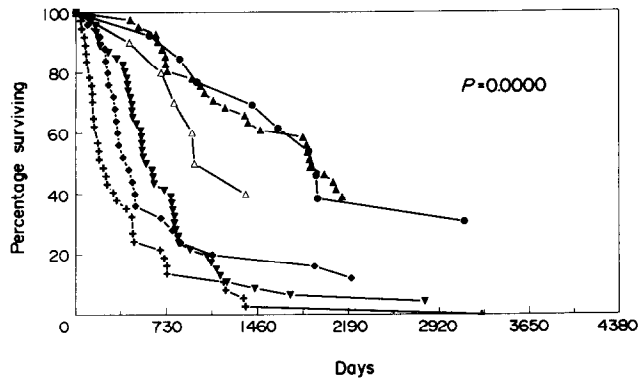

Fig. 5. Hexa-CAF and CHAP-5: survival in relation to type of response. △ = Complete remission documented by peritoneoscopy (10 entered; 6 died), ▲ = complete remission at laparotomy (41; 25), ● = microscopic disease (13; 9), ▼ = partial remission (46; 44), ◆ = no change (25; 22), + = progression (37; 37).

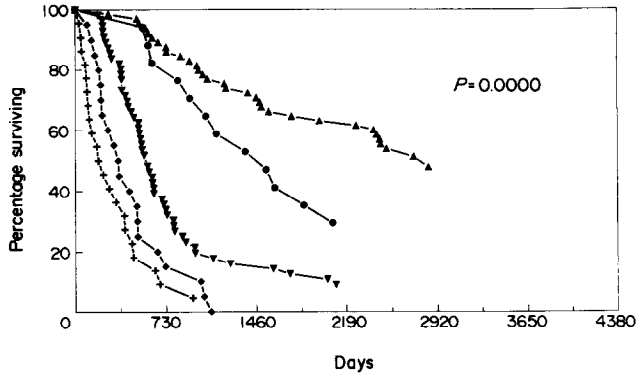

Fig. 6. CHAP-5 and CP. Survival in relation to type of response. ▲ = Complete remission documented at laparotomy (65 entered; 32 died), ● = microscopic disease (17; 12), ▼ = partial remission (56; 51), ◆ = no change (20; 20), + = progression (22; 21).

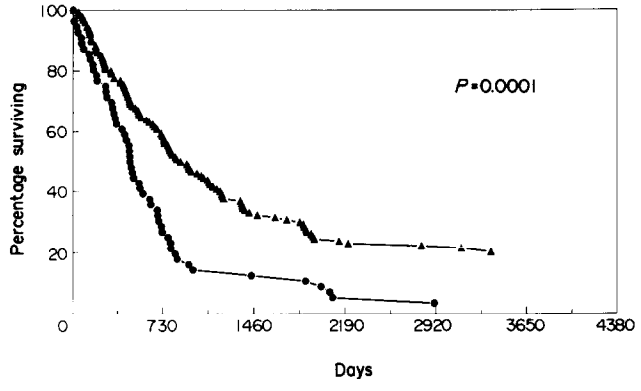

Fig. 7. Hexa-CAF and CHAP-5 survival in relation to FIGO stage. ▲ = FIGO stage III (130 entered; 103 died), ● = FIGO stage IV (56 entered; 54 died).

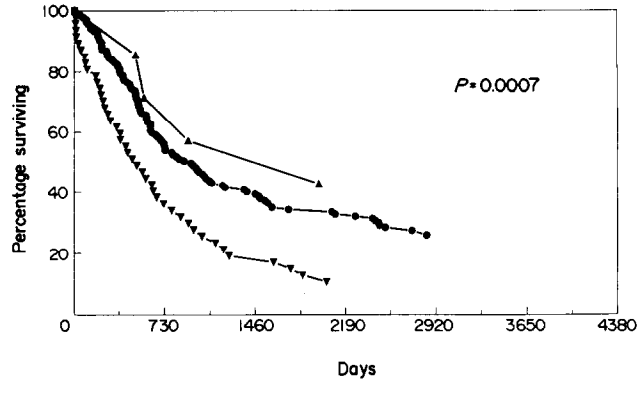

Fig. 8. CHAP-5 and CP. Survival in relation to FIGO stage. ▲ = FIGO stage IIb (7 entered; 4 died), ● = FIGO stage III (137; 100), ▼ = FIGO stage IV (47; 42).

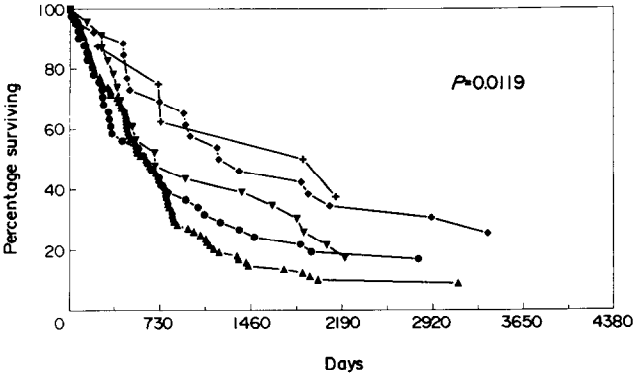

Fig. 9. Hexa-CAF and CHAP-5: survival in relation to the largest cross-sectional diameter prior to chemotherapy. ▲ = ≥5 cm (88 entered; 80 died), ● = 5–2 cm (41; 34), ▼ = 2–1 cm (23; 19), ◆ = <1 cm (26; 19), + = microscopic disease (8; 5).

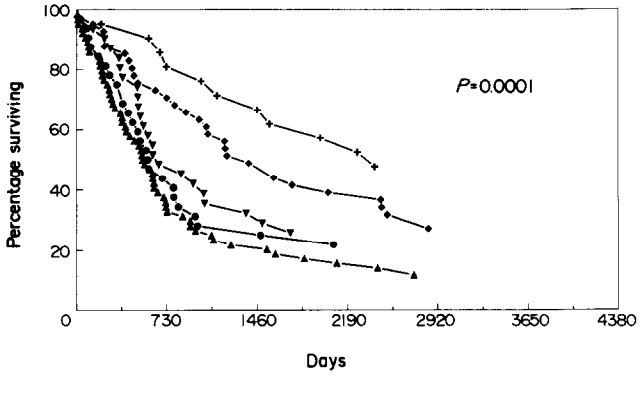

Fig. 10. CHAP-5 and CP: survival in relation to the largest cross-sectional diameter prior to chemotherapy. ▲ = ≥5 cm (64 entered; 56 died), ● = 5–2 cm (32; 25), ▼ = 2–1 cm (31; 23), ◆ = <1 cm (41; 29), + = microscopic disease (21; 11).

patients with stage IV disease will survive after 5 years and that this survival rate is probably not improved by adding cisplatin to the treatment regimen (Fig. 13). Another powerful factor predicting survival is the largest residual tumour diameter prior to cytotoxic treatment. As a result of this first analysis of both studies, it was found that the maximum size of residuum associated with a significant survival benefit was 1 cm or less. The survival for patients who had residual tumours with diameters between 1 and 2 cm was similar to that for patients who had larger tumour remnants [1, 2]. The present survival data show that these differences last even with longer follow-up. Although randomised trials have never been performed to

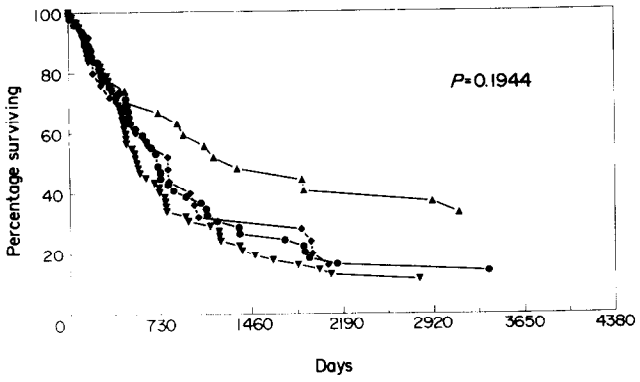

Fig. 11. Hexa-CAF and CHAP-5: survival in relation to Broders' grade. ▲ = Grade 1 (27 entered; 18 died), ● = grade 2 (49; 42), ▼ = grade 3 (62; 55), ◆ = grade 4 (25; 21).

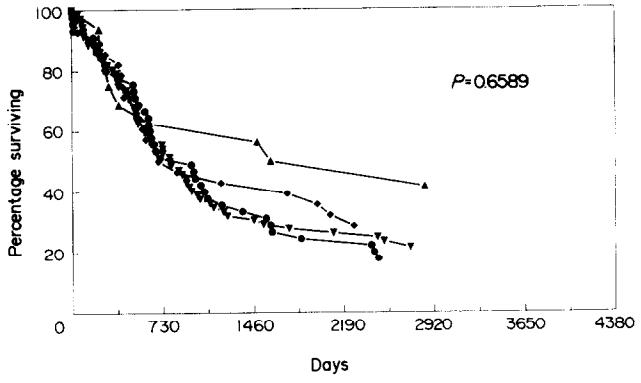

Fig. 12. CHAP-5 and CP. Survival in relation to Broders' grade. ▲ = Grade 1 (16 entered; 9 died), ● = grade 2 (43; 37), ▼ = grade 3 (72; 56), ◆ = grade 4 (28; 20).

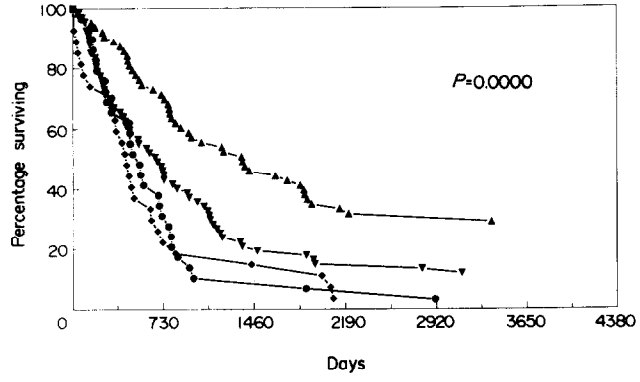

Fig. 13. Hexa-CAF and CHAP-5. Survival in relation to stage and treatment. ▲ = FIGO stage III, treatment CHAP-5 (63 entered; 44 died), ● = FIGO stage IV, treatment CHAP-5 (29; 28), ▼ = FIGO III, treatment Hexa-CAF (67; 59), ◆ = FIGO IV, treatment Hexa-CAF (27; 26).

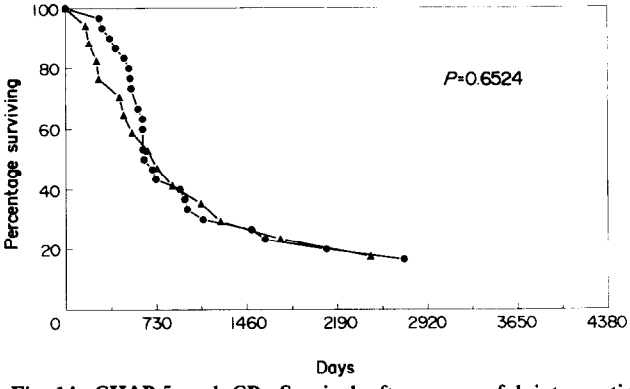

Fig. 14. CHAP-5 and CP. Survival after successful intervention surgery (≤1 cm) or attempted intervention surgery without successful removal of tumour (>1 cm). ▲ = >1 cm (17 entered; 14 died), ● = ≤1 cm intervention (30; 25).

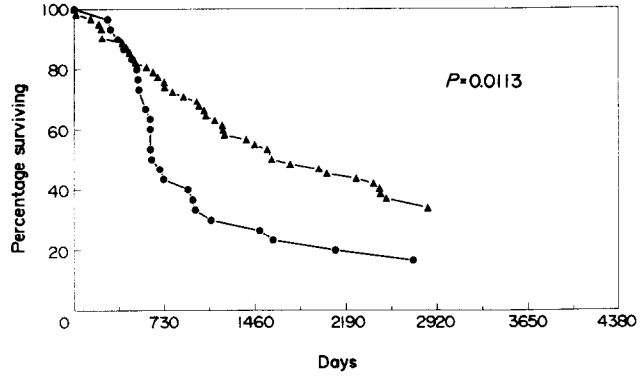

Fig. 15. CHAP-5 and CP. Survival after cytoreductive surgery leading to tumour residuals of ≤1 cm at the staging laparotomy (staging) or during chemotherapy (intervention cytoreductive surgery). ▲ = ≤1 cm staging (62 entered; 40 died), ● = ≤1 cm intervention (30; 25).

resolve the issue of the influence of primary cytoreduction on survival, the results suggest that primary cytoreductive surgery must be accepted as part of the treatment plan. The aim of the procedure is to minimise the tumour burden. It is not yet obvious from the literature whether the optimal margin for providing a significant survival benefit is 1, 1.5 or even 2 cm. Our results indicate that the debulking procedure can be classified as successful if the surgeon succeeds in removing all tumour exceeding 1 cm in diameter.

The benefits of intervention surgery are not yet established. We performed this type of surgery as soon as chemotherapeutic reduction rendered the tumour masses resectable. As presented in Fig. 14, successful intervention leaving residual tumour of less than 1 cm did not result in any long-term survival benefit. Survival was even worse than in patients who had successful cytoreduction before treatment started (Fig. 15). It is most likely that intervention surgery is only worthwhile in patients who have had a biopsy only at first surgery, but not in patients who have undergone a serious attempt at diagnostic laparotomy [2]. A randomised study of the EORTC to resolve this question is underway and the results will need to be taken into account before the role of intervention surgery as part of our standard treatment can be defined.

Cisplatin-based chemotherapy is the cornerstone in the treatment of advanced epithelial ovarian cancer. With the addition of cisplatin to an alkylating agent, about 80% of the patients respond and experience relief of symptoms and prolonged survival. Our studies prove that at 5 and 10 years a considerable number of patients may survive after receiving a cisplatin combination. In view of these results, caution should be exer-

cised about replacing cisplatin in combinations by carboplatin. Long-term data from comparative studies must equal the above reported results before a final decision can be made to replace cisplatin by carboplatin. So far, the CP regimen seems among the best regimens to be used for the treatment of epithelial ovarian cancer.

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Prognostic Value of c-*erb*B-2 Protein Expression in Human Lung Adenocarcinoma and Squamous Cell Carcinoma

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203 primary human lung tumours, of which 119 were adenocarcinoma and 84 were squamous cell carcinoma, were investigated immunohistochemically for the expression of c-*erb*B-2 protein. Positive staining was evident in 33 (28%) of adenocarcinomas and 2 (2%) of squamous cell carcinomas. In cases of adenocarcinoma, c-*erb*B-2 was present in 18% of those with stage I disease. In stage IIIA, stage IIIB and stage IV cases, c-*erb*B-2 was present in 39%, 50% and 60%, respectively (I vs. IIIA and I vs. IIIB: $P < 0.05$, I vs. IV: $P < 0.01$). The 5-year survival rates of c-*erb*B-2 positive patients and those who were negative were 30% and 52%, respectively, with a statistically significant difference ($P < 0.01$). These observations suggest that when the expression of c-*erb*B-2 correlates with invasiveness of the tumour, this correlation may serve as a prognostic indicator, particularly in cases of adenocarcinoma of the lung.
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INTRODUCTION

THE c-*erb*B-2 oncogene is related to the *neu* oncogene and was first identified in a chemically induced rat neuroblastoma [1]. This oncogene codes for a 185 kD transmembrane glycoprotein [2] with tyrosine kinase activity [3, 4] and is structurally similar to, but distinct from, epidermal growth factor receptor (EGFR) [2–5]. Amplification of the gene has been noted in various sites of adenocarcinoma [6] and is associated with lymph node involvement, relapse and survival in human breast cancer [7–9].

Recent investigations revealed that amplification of the c-*erb*B-2 gene correlates with immunohistological staining for c-*erb*B-2 protein [10, 12]. We have now examined c-*erb*B-2 protein expression, using an immunohistochemical method. For this we used adenocarcinoma and squamous cell carcinoma tissues of the human lung and searched for possible prognostic factors and different expressions of c-*erb*B-2.

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PATIENTS AND METHODS

Surgical specimens

We examined paraffin-embedded tissues obtained surgically from 203 patients with primary lung cancer, 119 of adenocarcinoma and 84 of squamous cell carcinoma. All patients had been diagnosed and treated in the Department of Surgery II of Kyushu University between 1974 and 1986. Patients who had died within the first post operative month or who had undergone