THE EFFECT OF DEBULKING SURGERY AFTER INDUCTION CHEMOTHERAPY ON THE PROGNOSIS IN ADVANCED EPITHELIAL OVARIAN CANCER

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Abstract *Background.* Although the value of primary cytoreductive surgery for epithelial ovarian cancer is beyond doubt, the value of debulking surgery after induction chemotherapy has not yet been defined. In this randomized study we investigated the effect on survival of debulking surgery.

Methods. Eligible patients had residual lesions measuring more than 1 cm in diameter after primary surgery. After three cycles of cyclophosphamide and cisplatin, these patients were randomly assigned to undergo either debulking surgery or no surgery, followed by further cycles of cyclophosphamide and cisplatin. The study end points were progression-free survival and overall survival. At surgery 65 percent of the patients had lesions measuring more than 1 cm. In 45 percent of this group, the lesions were reduced surgically to less than 1 cm.

Results. Of the 319 patients who underwent randomization, 278 could be evaluated (140 patients who underwent surgery and 138 patients who did not). Progression-free and overall survival were both significantly longer in the group that underwent surgery ($P = 0.01$). The difference in median survival was six months. The survival rate at two years was 56 percent for the group that underwent surgery and 46 percent for the group that did not. In the multivariate analysis, debulking surgery was an independent prognostic factor ($P = 0.012$). Overall, after adjustment for all other prognostic factors, surgery reduced the risk of death by 33 percent (95 percent confidence interval, 10 to 50 percent; $P = 0.008$). Surgery was not associated with death or severe morbidity.

Conclusions. Debulking surgery significantly lengthened progression-free and overall survival. The risk of death was reduced by one third, after adjustment for a variety of prognostic factors. (N Engl J Med 1995;332:629-34.)

THE value of cytoreductive surgery in the management of ovarian cancer has been debated for years. The reasons for cytoreductive surgery are manifold. Large tumors with relatively poor central blood supplies and the areas with the lowest growth rates are both rather insensitive to cytotoxic drugs.[1] In better-perfused small, residual tumors, the growth rate and the diffusion of chemotherapeutic agents are higher — factors that are apt to increase the efficacy of chemotherapy. The removal of large tumors also reduces the likelihood that drug-resistant clones will appear as a result of spontaneous mutations.[2] Moreover, small tumors require fewer cycles of chemotherapy, thus decreasing the probability of drug-induced resistance.

Several nonrandomized studies showed improved survival of patients with residual tumors less than 1 cm in diameter after primary surgery, as compared with patients with larger lesions.[3-5] In a case–control study of patients with minimal residual disease, Eisenkop et al. reported that patients whose small lesions were all resected survived significantly longer than patients in whom such lesions were not resected.[6] On the other hand, Hacker et al.[7] and Hoskins et al.[8] reported that despite optimal cytoreduction, the survival of patients with large intraabdominal metastases before resection was significantly worse than that of patients with small initial intraabdominal lesions. These results suggest that in addition to residual disease after cytoreduction, intrinsic tumor factors are of prognostic importance. They also raise the question of whether cytoreduction has a significant effect on survival among patients with the same size tumors and the same intrinsic prognostic factors.

The value of debulking surgery after induction chemotherapy is even more difficult to assess. Several studies indicated that patients in whom cytoreduction was optimal after induction chemotherapy had approximately the same survival rate as patients in whom cytoreduction was optimal at primary surgery.[9-12] Neijt et al., however, reported just the opposite.[4,13] Patients with optimal cytoreduction at intervention surgery had poorer rates of survival than patients with optimal cytoreduction at primary surgery. Moreover, the survival of patients with optimal cytoreduction at intervention surgery was the same as that of patients with suboptimal cytoreduction. All these studies, however, included only small numbers of patients with different prognoses.

In 1987 the Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) initiated a randomized phase 3 study to establish the effect on survival of debulking surgery after induction chemotherapy.

METHODS

Selection of Patients, Study Design, and Evaluation Methods

From March 1987 to May 1993, 425 patients were enrolled in the study. Eligible patients had to have biopsy-proved epithelial ovarian carcinoma with an International Federation of Gynecology and Obstetrics stage of IIb to IV,[14] residual lesions measuring more than 1 cm in diameter, a World Health Organization (WHO) performance

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*Other principal investigators who contributed to the study are listed in the Appendix.

status of 0 to 2,[15] an age of less than 75 years, and adequate bone marrow and renal function, and they had to have undergone primary surgery no more than six weeks before treatment began. Clinical response was assessed according to the standard WHO response criteria.[15] A complete response was defined pathologically as the absence of macroscopic and microscopic tumor at surgery. Optimal cytoreduction was defined as the reduction of all tumor lesions to less than 1 cm in diameter.

The study design is shown in Figure 1. All eligible patients, after giving informed consent, were registered centrally at the EORTC Data Center before chemotherapy was begun. The patients received three cycles of cyclophosphamide at a dose of 750 mg per square meter of body-surface area, and cisplatin at a dose of 75 mg per square meter every three weeks. After the third and sixth cycles, a clinical evaluation was performed consisting of a gynecologic and general physical examination, computed tomography or sonography (or both), and measurement of serum CA-125. After the third cycle, patients with tumor progression or a contraindication to surgery were removed from the study. Patients with a clinical response or stable disease were randomly assigned to undergo debulking surgery or not to undergo surgery. Randomization was done centrally at the EORTC Data Center after stratification with a minimization technique to account for institution, performance status, and clinical response.

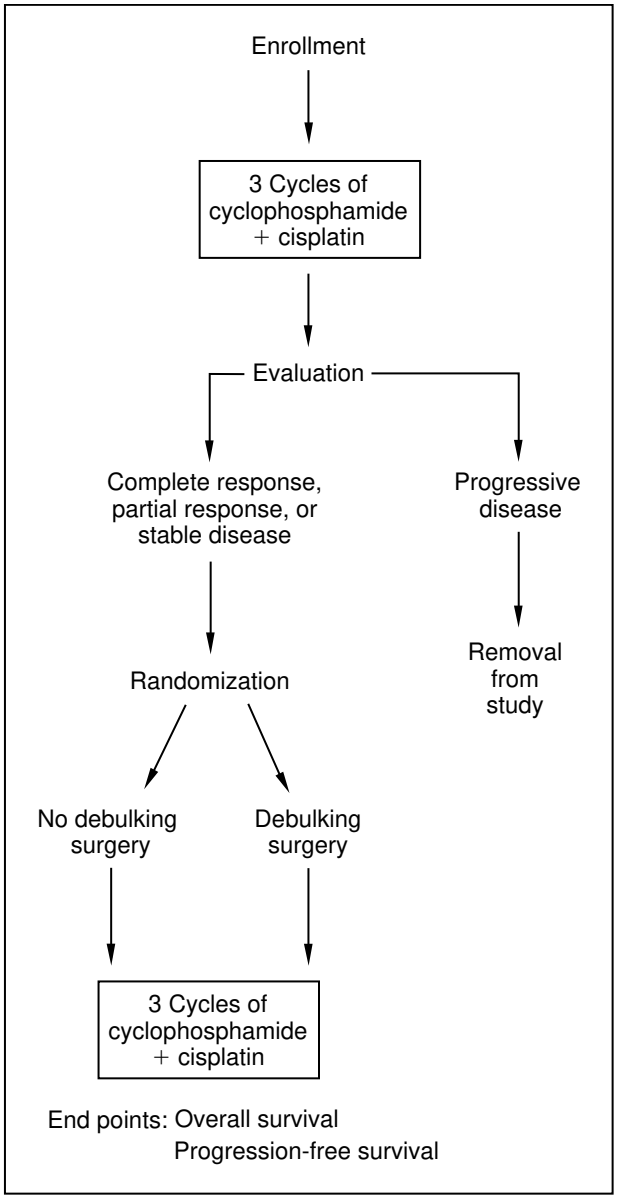

Figure 1. Design of the Study.

At surgery, scheduled within 28 days after the third cycle of chemotherapy, maximal cytoreduction was performed and, if not done previously, a bilateral salpingo-oophorectomy, hysterectomy, and infracolic omentectomy were carried out when possible. Chemotherapy was to be resumed within four weeks after surgery. All randomized patients were scheduled to receive at least six cycles of cyclophosphamide and cisplatin unless this therapy was clearly contraindicated. The decision to continue or discontinue treatment after the sixth cycle was based on the policy of the center. Patients with a complete clinical response preferably had a "second-look" operation regardless of whether they had undergone debulking surgery. After therapy patients were seen every two months during the first two years and indefinitely thereafter according to each center's policy. The end points of the study were overall survival and progression-free survival.

Statistical Analysis

An accrual target of 440 randomized patients was specified in the protocol in order for the study to have an 80 percent probability of detecting a 30 percent reduction in the risk of death, with the use of a two-tailed log-rank test at the conventional 5 percent level of significance.[16] No formal statistical rules were specified in the protocol for interim analyses, which were performed once a year according to EORTC policy.[17] A difference in survival first emerged in September 1991 ($P=0.006$). This difference was confirmed by further interim analyses in October 1992 ($P=0.016$), February 1993 ($P=0.028$), and April 1993 ($P=0.012$), at which time the group decided to stop enrolling patients in the study. Follow-up was continued on all randomized patients.

Survival was calculated from the day chemotherapy was begun until death, regardless of the cause of death. Progression-free survival was calculated from the day chemotherapy was begun to the time of progression or death. All randomized patients with some follow-up information were included in the analyses of survival and progression-free survival, which were performed strictly according to the intention-to-treat principle. Survival and progression-free survival curves were calculated for each treatment group with Kaplan–Meier estimates[18] and compared with the log-rank test.[19] Stratified analyses and Cox regression analyses were performed to adjust treatment comparisons for all known prognostic factors.[20]

Results

Recruitment and Demographic Characteristics of the Patients

Of the 425 patients enrolled in the study, 319 patients underwent randomization. One hundred six patients did not undergo randomization for the following reasons: 39 had disease progression, 22 had a contraindication to surgery, 17 were still receiving induction chemotherapy, 11 died, 10 declined to participate in the study, 4 were found to be ineligible, and 3 were lost to follow-up.

At the time of the analysis follow-up data were available on 278 of the 319 randomized patients: 140 patients who were assigned to undergo debulking surgery and 138 who were assigned not to undergo surgery. All known prognostic characteristics were well balanced between the two treatment groups (Table 1). The patients ranged in age from 32 to 74 years, with a median age of 59 years in both groups.

Treatment Received

Treatment data were available for all 278 patients. Ninety-three percent of the patients (130 patients) assigned to undergo surgery had had surgery, and 100 percent of the patients (138 patients) assigned not to undergo surgery had had no surgery. In both groups 84 percent of the patients received at least six cycles of cy-

Table 1. Characteristics of the Patients.

Characteristic	Debulking Surgery (N = 140)	No Debulking Surgery (N = 138)
	percent	
WHO performance status		
0	34	34
1	48	51
2	18	15
FIGO stage*		
IIb	6	4
III	71	75
IV	23	21
Histologic type		
Serous	59	56
Mucinous	8	4
Endometrioid	7	10
Clear cell	1	4
Unclassified	25	26
Tumor grade		
1	8	9
2	27	32
3	61	54
Unknown	4	5
Tumor size		
1–2 cm	6	4
>2–5 cm	25	20
>5–10 cm	20	24
>10 cm	28	32
Unknown, >2 cm	21	20
No. of lesions		
1–5	35	35
6–10	22	15
>10	43	50
Ovary in situ		
Yes	29	31
Unknown	18	18
Peritoneal carcinomatosis		
Yes	46	43
Unknown	23	23
Ascites	78	72
Response after 3 cycles of cyclophosphamide and cisplatin		
Complete response	18	17
Partial response	54	55
Stable disease	28	28

*FIGO denotes International Federation of Gynecology and Obstetrics.

clophosphamide and cisplatin. A reduction in the dose or postponement of chemotherapy was necessary in 36 percent and 48 percent of the patients who had had surgery and in 37 percent and 49 percent of the patients who had not undergone surgery, respectively. The length of time from cycle 4 to cycle 6 was similar in both treatment groups ($P = 0.42$), lasting a median of seven weeks in each. The median overall duration of treatment from cycle 1 to cycle 6 was 21 weeks for the patients who had had surgery and 17.5 weeks for the patients who had not had surgery.

The reasons for stopping chemotherapy after randomization and before the sixth cycle in the group that had undergone surgery and in the group that had not were as follows: progressive disease in 5 and 3 percent, respectively; toxic reactions in 3 and 2 percent, respectively; refusal to continue chemotherapy in 4 and 5 percent, respectively; and unknown in 4 and 6 percent, respectively. Consolidation chemotherapy after the sixth cycle was given to 36 percent of the patients who had undergone surgery and 51 percent of those who had not had surgery. A second-look operation was performed in 52 patients who had undergone surgery and 51 patients who had not.

Results of Debulking Surgery

Surgical data were available on 127 of the 130 patients who underwent debulking surgery. At laparotomy, 83 of the 127 patients (65 percent) had tumors that exceeded 1 cm in diameter and 44 patients had tumors that had been reduced to less than 1 cm by chemotherapy (Table 2). In 37 of the 83 patients (45 percent) with lesions measuring more than 1 cm, the tumors were reduced by surgery to a diameter of less than 1 cm. In the other 46 patients an attempt was made to perform maximal cytoreduction, but lesions measuring more than 1 cm had to be left behind. The ovaries were resected in 32 of 41 patients (78 percent) whose ovaries were still in situ. Overall, 81 of the 127 patients (64 percent) had residual lesions of less than 1 cm after debulking surgery.

No lethal or serious complications were observed after debulking surgery. The intraoperative complications consisted of bowel injury in 3 percent of the patients and bladder injury in 2 percent. Twenty-two percent lost more than 500 ml of blood. The postoperative complications consisted of fever (temperature of more than 38.5°C on more than two days) in 4 percent, ileus for more than five days in 1 percent, urinary tract infection in 4 percent, wound infection in 2 percent, deep venous thrombosis in 1 percent, and lung embolism in 2 percent. These complications were similar in kind and severity to those observed at primary surgery.

Clinical Response

The overall rate of clinical response after the sixth cycle of chemotherapy was 84 percent for the group that underwent debulking surgery and 70 percent for the group that did not undergo surgery; the rate of complete response was 70 percent and 35 percent, respectively. The disease progressed in 8 percent of the patients who underwent debulking surgery and 12 percent of those who did not.

Before second-look surgery, 79 percent of the patients who had undergone debulking surgery had a complete clinical response, as compared with 59 percent of the patients who did not have debulking surgery. Second-look surgery in the patients who had undergone debulking surgery and in those who had not revealed similar rates of complete response (37 percent vs. 33 percent), partial response (28 percent vs. 37 percent),

Table 2. Results of Debulking Surgery after Three Cycles of Cyclophosphamide and Cisplatin.

Largest Lesions before Debulking Surgery	Total	Largest Lesions after Debulking Surgery		
		No Macroscopic	<1 cm	≥1 cm
No macroscopic lesions	22	22	0	0
<1 cm	22	7	15	0
≥1 cm	83	19	18	46
Total	127	48	33	46

stable disease (2 percent vs. 6 percent), disease progression (8 percent vs. 6 percent) and microscopic disease (15 percent vs. 10 percent), and similar percentages of patients whose response could not be evaluated (10 percent vs. 8 percent). The size of the tumors before cytoreduction and after cytoreduction at second-look surgery is shown in Table 3.

Survival and Progression-free Survival

At the time of the analysis, 75 percent of the patients had been followed for more than 2.2 years, 50 percent for more than 3.5 years, and 25 percent for more than 4.3 years. The maximal follow-up was 5.6 years. Both overall survival and progression-free survival were significantly longer ($P=0.01$) for the patients who underwent debulking surgery. In addition, the three most recent interim analyses had shown a significant benefit of surgery. The difference in survival was more substantial when patients with stage IV disease were excluded ($P=0.003$ for overall survival and $P=0.002$ for progression-free survival).

The median survival was 26 months for the patients who underwent debulking surgery and 20 months for those who did not. The proportion of patients alive at two years was 56 percent in the former group and 46 percent in the latter group (Fig. 2). Overall, surgery reduced the unadjusted risk of death by 31 percent (the hazard rate, or the risk of death at any given moment). The beneficial effect of surgery on survival was consistent throughout the observation period. Figure 3 shows the survival curves for the patients who did not undergo debulking surgery and for the patients who did undergo debulking surgery according to the size of residual lesions at the time of surgery. Patients whose lesions measured less than 1 cm before cytoreduction survived significantly longer (median, 41.6 months; $P<0.001$) than patients whose lesions measured more than 1 cm after debulking surgery (median survival, 19.4 months); survival in the latter group was similar to overall survival in the group that did not undergo debulking surgery (median survival, 20.0 months). Patients with optimal cytoreduction (whose remaining lesions measured less than 1 cm) also survived significantly longer (median survival, 26.6 months; $P=0.04$) than patients with suboptimal cytoreduction.

The median progression-free survival was 18 months for the patients who had debulking surgery and 13 months for the patients who did not have debulking surgery. The percentage of patients alive and free of progressive disease at two years was 38 percent in the former group and 26 percent in the latter (Fig. 4).

Table 3. Size of the Tumors before Cytoreduction and after Cytoreduction at Second-Look Surgery.

Size of Tumor	Debulking Surgery (N = 52)		No Debulking Surgery (N = 51)	
	Before cytoreduction	After cytoreduction	Before cytoreduction	After cytoreduction
	no. of patients			
No macroscopic lesions	27	37	22	30
<1 cm	13	9	5	6
≥1 cm	7	1	20	11
Unknown*	5	5	4	4

*No information was available for nine patients.

Figure 2. Survival of Patients with Advanced Epithelial Ovarian Cancer According to Whether They Underwent Debulking Surgery.
$P=0.012$ for the comparison between the groups by the log-rank test.

Figure 5 shows the progression-free survival curves for the patients who did not have debulking surgery and for the patients who did have debulking surgery, according to the size of the residual lesions at the time of surgery. The progression-free survival of patients whose lesions were less than 1 cm in diameter before cytoreduction was significantly longer (median, 24.1 months; $P<0.001$) than that of patients with suboptimal cytoreduction (median survival, 12.1 months); results for the latter were similar to the progression-free survival seen in the group that did not have debulking surgery (median survival, 12.9 months). Likewise, the progression-free survival of patients with optimal cytoreduction was significantly longer (median survival, 23.3 months; $P=0.003$) than the progression-free survival of patients with suboptimal cytoreduction.

Adjusted and Multivariate Analyses

Table 4 shows the effect of adjusting the comparison of survival between the two treatment groups for all known prognostic factors. The 31 percent reduction in the risk of death derived from the unadjusted comparison (95 percent confidence interval, 8 to 49 percent) remained qualitatively unchanged by all adjustments for prognostic factors (risk reductions ranging from 29 to 36 percent). The relative benefit of surgery was remarkably consistent across all subgroups of patients (data not shown). When all prognostic factors were taken into account simultaneously in a Cox regression model, the reduction in the risk of death due to surgery was 33 percent (95 percent confidence interval, 10 to 50 percent; $P=0.008$). When the population of patients was subdivided into two equal groups on the basis of the multivariate risk, there was

no evidence that the relative benefit of debulking surgery was different for the high-risk and the low-risk patients.

Discussion

Our study establishes the effect of tumor reduction on progression-free and overall survival, which were both significantly prolonged in patients randomly assigned to undergo debulking surgery. The median progression-free survival and overall survival were increased by five and six months, respectively. Moreover, the beneficial effect of surgery on progression-free and overall survival was consistent throughout the observation period (with a median follow-up of 3.5 years). However, much longer follow-up is clearly needed before the curative value of debulking surgery can be assessed.

The majority of the studies in the literature compared the survival of patients after optimal cytoreductive surgery with the survival of patients after suboptimal cytoreduction.[3-5,9-11] All these studies are hampered by the unavoidable and serious bias inherent in the comparison of patients with different prognostic factors. Only one other prospective randomized study has addressed the question of the value of cytoreduction.[21] In the interim analysis there was no significant difference in survival between the group that underwent surgery (median survival, 23 months) and the group that did not (median survival, 16 months). Only 34 patients in each group were evaluated, however.

In our study patients with lesions of less than 1 cm at debulking surgery before or after cytoreduction survived longer than patients with larger residual lesions (Fig. 3). Nonetheless, the survival of patients with residual lesions of more than 1 cm after surgery — the patients with the poorest prognosis — was not significantly different from the survival of the patients who did not undergo debulking surgery. The fact that survival was similar in these two groups means either that patients with suboptimal cytoreduction did benefit from cytoreduction or that there were patients in the group that did not undergo debulking surgery who might have benefited from cytoreductive surgery. Qualitatively, the same observations were made for progression-free survival (Fig. 5).

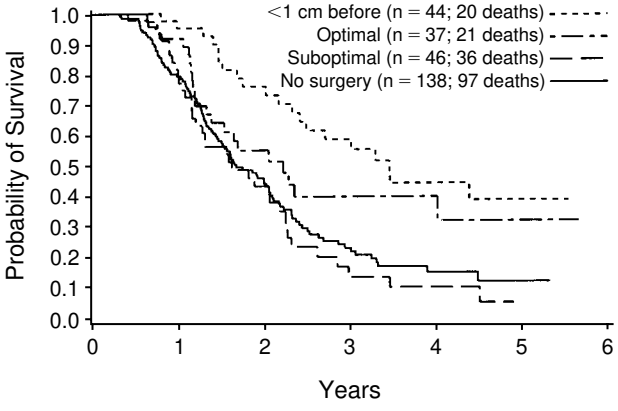

Figure 3. Survival of Patients with Advanced Epithelial Ovarian Cancer Who Did Not Have Debulking Surgery and Patients Who Had Such Surgery, According to Whether the Lesions Were Less Than 1 cm in Diameter before Cytoreduction, Less Than 1 cm after Cytoreduction (Optimal), or More Than 1 cm after Cytoreduction (Suboptimal).

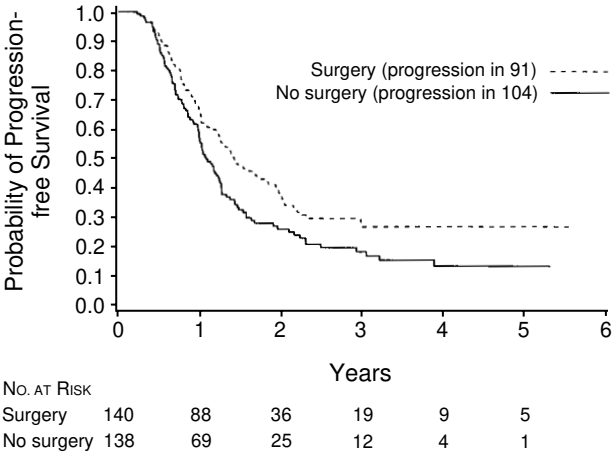

Figure 4. Progression-free Survival of Patients with Advanced Epithelial Ovarian Cancer According to Whether They Underwent Debulking Surgery.
P = 0.013 for the comparison between the groups by the log-rank test.

We also attempted to identify a group of patients who did not benefit from debulking surgery. In the multivariate analysis, the benefit of surgery remained significant even after adjustment for all other known prognostic factors (33 percent reduction in the risk of death, P = 0.008). When the patients were subdivided into high-risk and low-risk groups on the basis of either individual prognostic factors or the multivariate risk, there was no difference in the relative benefit of surgery between the two groups. Thus, we could not identify a subgroup of patients who clearly did not benefit from

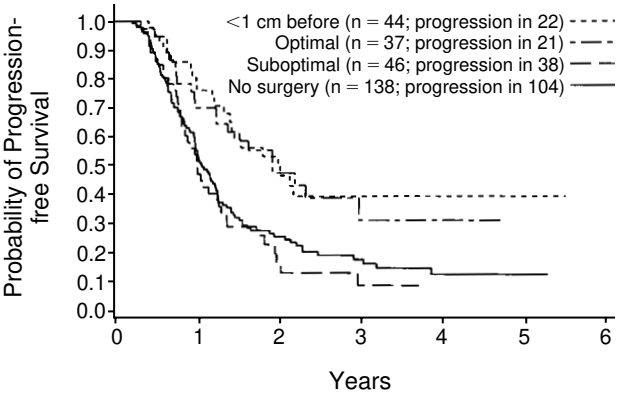

Figure 5. Progression-free Survival of Patients with Advanced Epithelial Ovarian Cancer Who Did Not Have Debulking Surgery and Patients Who Had Such Surgery, According to Whether the Lesions Were Less Than 1 cm in Diameter before Cytoreduction, Less Than 1 cm after Cytoreduction (Optimal), or More Than 1 cm after Cytoreduction (Suboptimal).

Table 4. Analysis of the Risk of Death after Debulking Surgery.

Analysis	Risk Reduction	P Value
	%	
Unadjusted	31	0.012
Univariate		
No. of lesions	36	0.003
Ascites	35	0.004
Tumor grade	34	0.006
Response after 3 cycles of cyclophosphamide and cisplatin	33	0.006
WHO performance status	32	0.011
FIGO stage*	29	0.026
Multivariate (Cox regression model)	33	0.008

*FIGO denotes International Federation of Gynecology and Obstetrics.

debulking surgery or a subgroup of patients in whom the benefit was much larger than the overall benefit. This, of course, does not imply that all patients do benefit from intervention surgery, but it does underline the need for further investigations.

In an attempt to exclude other factors that might have influenced the prognosis of the patients who underwent surgery, we evaluated the overall dose of chemotherapy and the degree of tumor reduction at second-look surgery. The total number of cycles of cyclophosphamide and cisplatin and the number of patients who required reductions in the doses were identical in both groups. Also, the percentages of patients who underwent optimal cytoreduction at second-look surgery and of patients who underwent consolidation therapy were similar. Therefore, even if there had been a benefit in terms of survival from cytoreduction at second-look surgery or from consolidation chemotherapy, such a benefit would have affected both treatment groups about equally.

Debulking surgery was not associated with death or severe morbidity. Intraoperative complications were observed in 5 percent of the patients. Mild postoperative complications were observed in 14 percent of the patients, a figure that is comparable to the rates of postoperative complications observed in other studies.[12,22-24] In addition, surgery did not have a negative effect on postoperative chemotherapy. Thus, we believe that the six-month increase in median survival among the patients who underwent surgical debulking outweighs the morbidity associated with surgery.

We are indebted to A. Pawinsky of the EORTC Data Center for help in the final analysis of the data, to F. Smits for assistance in the preparation of the manuscript, and to all the gynecologists and medical oncologists who are not mentioned here by name but who participated in the study.

Appendix

The following principal investigators also contributed to the study: M.A. Nooy (Academisch Ziekenhuis Leiden, Leiden, the Netherlands), A. Cervantes (University Hospital Valencia, Valencia, Spain), J.B. Vermorken (Academisch Ziekenhuis der Vrije Universiteit, Amsterdam), G. Bolis (University of Milan, Milan, Italy), L.V.A.M. Beex (St. Radboud Ziekenhuis, Nijmegen, the Netherlands), C.F. de Oliveira (Instituto Portugues Ontologica Coimbra, Coimbra, Portugal), C. Madronal (Instituto d'Oncologia de Corachan, Barcelona, Spain), K.J. Roozendaal (Onze Lieve Vrouwe Gasthuis, Amsterdam), A. Poveda (Instituto Valenciano de Oncologia, Valencia, Spain), M.T. Osorio (Instituto Portugues de Oncologia de Francisco Gentil, Porto, Portugal) P. Zola (Ospedale Santa Anna, Turin, Italy), J.A. Wijnen (St. Clara Hospital, Rotterdam, the Netherlands), M.J. Piccart (Institute Jules Bordet, Brussels, Belgium), and A. van de Gaast (University Hospital Dijkzigt, Rotterdam, the Netherlands).

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