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A Meta-analysis of Prognostic Factors in Advanced Ovarian Cancer with Median Survival and Overall Survival (Measured with the Log (Relative Risk)) as Main Objectives

E.E. VOEST,* J.C. VAN HOUWELINGEN† and J.P. NEIJT*

**Utrecht University Hospital, Department of Oncology, Catharijnesingel 101, 3511 GV Utrecht, The Netherlands and †Leiden University, Department of Medical Statistics, The Netherlands*

Abstract—*We performed a meta-analysis of 38 articles containing 66 treatment groups and 3443 patients in order to evaluate prognostic factors in advanced epithelial ovarian cancer. To evaluate overall survival we designed a method to summarize the overall survival curve into one single figure: the log (relative risk) (LRR). This is the first meta-analysis using overall survival (measured with the LRR) as an objective.*

We found that the main prognostic factors predicting an improved survival (measured with the LRR) are: chemotherapy including cisplatin as initial treatment, a residual tumour mass of less than 2 cm prior to therapy, FIGO stage II/III and a good performance status. In a multivariate model, the use of cisplatin and the residual tumour were found to be the only factors of prognostic relevance. No relation between median survival and the overall clinical response rate of all patients entered in the denominator, could be demonstrated. Undifferentiated tumours and patients treated with cisplatin regimens had higher response rates to treatment but younger patients and those with endometrioid histology were less likely to respond. A surgical complete remission was encountered more frequently among studies that included a high number of patients with small tumour masses prior to treatment.

Trials using cisplatin included more patients with small tumour nodules in their patient material compared to studies not using this drug. The data illustrate the danger of comparing studies with each other. In the trials with a high percentage of patients with small tumour residuals in the study population more toxic deaths were seen. This probably reflects the fact that they had received more intensive treatment.

The LRR correlated strongly with the median survival, response and the percentage of surgical complete remissions. We concluded that the introduction of the LRR can be a meaningful addition to the evaluation of the influence of prognostic factors on overall survival.

INTRODUCTION

AFTER the introduction of cispatin in combination regimens for the treatment of ovarian cancer the results of treatment of the advanced stages of this disease have been improved [1, 2]. The outcome of treatment is not only determined by the treatment itself, but also by a number of other variables. Many investigators have emphasized the importance of recognition of these factors for treatment planning and stratification in clinial trials [3–8]. We searched for prognostic factors in ovarian cancer by combining the results of previous reports, a type of research called meta-analysis [9, 10]. Studies in ovarian cancer use the response rate, median survival, the rate of complete remissions at second-look surgery, and overall survival as main objectives. For these reasons we performed a meta-analysis of clinical trials in previously untreated advanced ovarian cancer, looking for prognostic factors that correlate with all these parameters. Another study objective was to test a new parameter determined by overall survival: the log (relative risk) (LRR). This parameter makes it possible to reduce the whole survival curve to one single figure. This appears more accurate than the use of a 5 year survival rate which is only a single point in the entire survival curve.

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Correspondence and requests for reprints should be addressed to: J.P. Neijt, M.D., Utrecht University Hospital, Department of Oncology, Catharijnesingel 101, 3511 GV Utrecht, The Netherlands.

MATERIALS AND METHODS

Selection of papers

Papers for analysis were selected from journals in the English language literature. Only studies which met the following criteria were included:

All studies reported on:

(1) patients with FIGO stage IIb, III and IV epithelial ovarian carcinoma,
(2) prospectively treated patients entered in a phase III study,
(3) patients without previous hormonal or chemotherapy at entry,
(4) no more than 10% of patients treated with previous radiotherapy,
(5) a registered median survival or a survival curve in the final publication.

Only full papers were used, abstracts were excluded. No articles were excluded because of the final results published. All articles were selected and reviewed by two investigators.

Statistical methods

Correlations between the prognostic factors were calculated with the Pearson correlation matrix. In our statistical analysis we used percentages of the total number of patients entered in each treatment arm, not the absolute patient number. In this way we used a model for the variability between studies. A multiple regression model was used to find relevant prognostic variables independent of each other. The median survival and LRR were taken as endpoints for the analysis.

Log (relative risk) (LRR)

Since median survival is a relatively short term figure we designed a method to use the complete survival curve compressed in one single number in our statistical analysis. We introduced the log (relative risk) (LRR) as such a long term survival figure. Computation of LRR is based on the assumption of proportional hazards that is also used in the Cox regression model. Proportional hazards are equivalent with parallel curves in the log (−log(survival)) plot (survival expressed as a fraction, not as a percentage). In Fig. 1 all log (−log(survival)) curves of 59 treatment groups evaluated are plotted. They are fairly parallel. Using these curves, an average curve is computed. For each regimen the mean distance between its log (−log(survival)) curve and the average curve is computed (see Fig. 2). This yields the LRR index for that given regimen. The translation to ordinary survival curves is given in Fig. 3. Notice the reverse order of the curves; the two lowest curves in Fig. 2 represent the two upper survival curves. $F_x(t)$ denotes the 'average' survival curve. For an arbitrary regimen the 'theoretical' curve is given by $F(t) = F_x(t)^{RR}$, where $RR = e^{LRR}$.

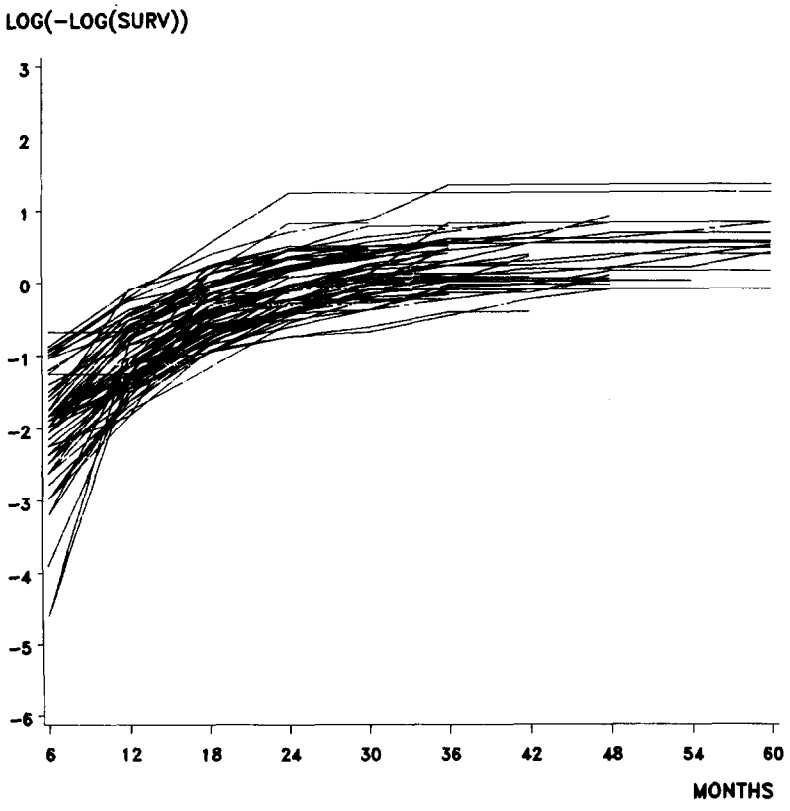

Fig. 1. The log (−log (survival)) curves of 59 treatment groups. Every curve represents a transformed survival curve by means of the formula: $\log\left(-\log\frac{surv\%}{100}\right)$.

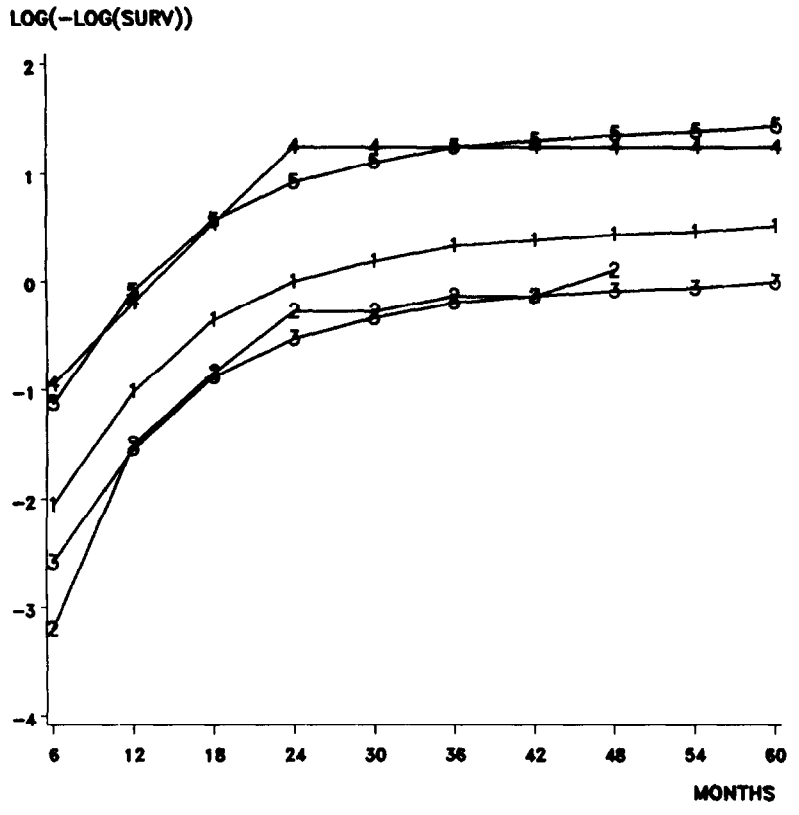

Fig. 2. Calculation of the log (relative risk) 'LRR' for two log (−log(survival)) curves. The mean distance between the 'average' curve and the log (−log(survival)) curves presents the mean LRR. The example curves are chosen as representatives of better and worse survival curves. Curve 1: average log (−log(survival)) curve of all regimens. Curve 2: observed log (−log(survival)) curve of CAP regimen [14]. Curve 3: theoretical log (−log(survival)) curve as calculated from the mean LRR. Curve 4: observed log (−log(survival)) curve of a cyclophosphamide monotherapy regimen [16]. Curve 5: theoretical log (−log(survival)) curve as calculated from the mean LRR.

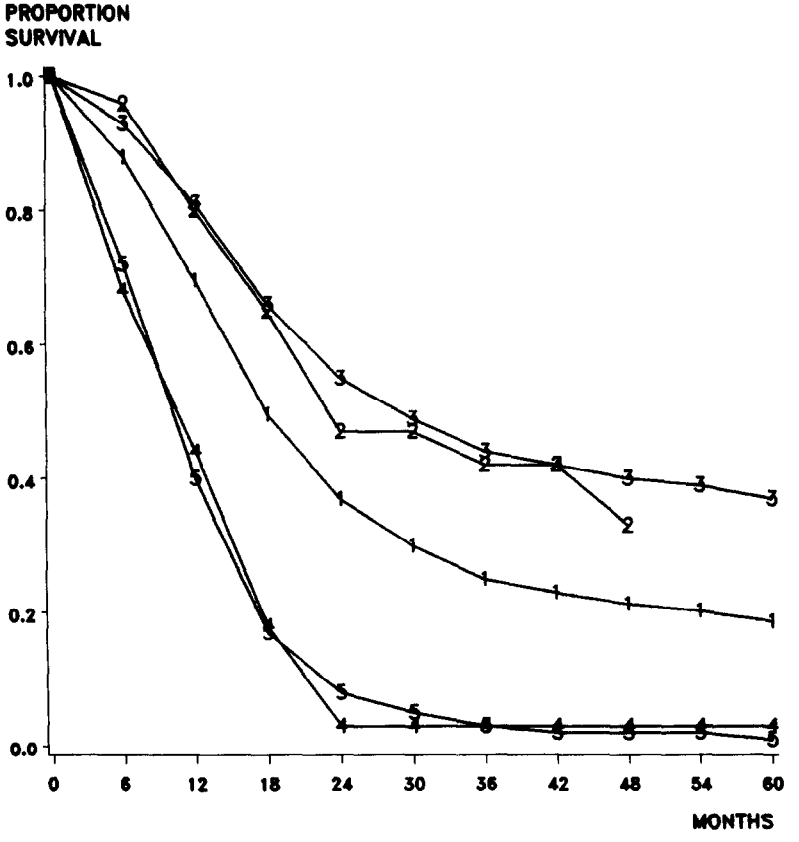

Fig. 3. The transformation to ordinary survival curves of the curves in Fig. 2. Curve 1: average survival curve of all regimens. Curve 2: observed survival curve of a CAP regimen [14]. Curve 3: theoretical survival curve as calculated from the mean LRR. Curve 4: observed survival curve of a cyclophosphamide monotherapy regimen [16]. Curve 5: the theoretical survival curve as calculated from the mean LRR.

In Table 1 an example calculation is given for the LRR of a survival curve. The survival percentages of the average curve are given in the second column. While the survival percentages of the example curve are in the fourth column. By subtracting the log (−log(survival)) values and calculating the average this yields the LRR for the example curve. A more negative LRR correlates with a better overall survival. The LRR of the example curve is −0.52.

Registration of factors analysed

In each study we registered the drugs that were used in combination or alone. The agents are summarized at the end of Table 2.

Where articles used the Broders grading system we registered a Broders grade 1 as a well differentiated tumour; Broders grade 2 as moderately differentiated and Broders grade 3 and 4 as poorly differentiated. The histological type was divided between serous, mucinous, endometrioid, clear cell, undifferentiated, unclassified and missing.

In evaluating residual tumour prior to chemotherapy we divided the patients in two groups: patients with residual tumour of more or less than 2 cm in cross section.

Performance status was only registered in 19 treatment arms. When data were presented according to the Karnofsky scale we translated them to the scale used by the Eastern Cooperative Oncology Group (ECOG): Patients with a Karnofsky index of 100 (able to carry out all normal activity without restriction) were classified as 0; patients with a Karnofsky index of 90 or 80 (restricted in physically strenuous activity but ambulatory and able to carry out light work) as 1; those with a Karnofsky index of 70 or 60 (ambulatory and capable of all self-care but unable to carry out any work, up and about more than 50% of waking hours) as 2. Patients with a Karnofsky index of less than 60 (capable of only limited self-care, confined to bed or chair for more than 50% of waking hours) were classified as 3.

Countries in which the trials took place were divided in two groups: (1) North America; (2) Europe and others.

FIGO stage registration was divided into two groups as well: stage IIb and III versus stage IV.

Toxicity was defined as the presence of chemotherapy related deaths. Evaluation of toxicity by means of the ECOG scale was impossible because of the inconsistency of presented data.

We measured survival rates at intervals of 6 months from the survival curve published in the article. The influence of salvage treatment was not taken into account.

Definitions of tumour response

A complete clinical remission was defined as complete regression of all clinically detectable tumour, determined by two observations not less than 4 weeks apart. A partial remission was defined as a decrease of more than 50% in measurable lesions with or without a complete regression of malignant effusions. A complete surgical remission was defined as an absence of gross detectable tumour and washings, and multiple biopsy specimens were negative for tumour. Overall response includes complete and partial response determined clinically or after surgicopathological restaging. Overall response rate (all patients entered) means that in the denominator the total number of patients eligible for study was used. Overall response rate (all patients evaluated) is a response rate calculated from a denominator including the total number of patients evaluable for response.

RESULTS

The distribution of patient characteristics in the publications analysed are summarized as mean

Table 1. Calculation of LRR by means of an example survival curve. The LRR for the example curve is found by subtracting the log (−log(survival)) values of the example and average curve and calculating the average. The LRR in this example (the mean of the values in the last column) is −0.52

Time period after start chemotherapy	Average survival curve		Example survival curve		Difference of the average and example curve
	Survival rate	Log (−log(survival))	Survival rate	Log (−log(survival))	
6 months	88%	−2.05	96%	−3.20	−1.15
12 months	70%	−1.01	80%	−1.50	−0.49
18 months	50%	−0.36	65%	−0.84	−0.49
24 months	37%	−0.00	47%	−0.28	−0.28
30 months	30%	0.19	47%	−0.28	−0.47
36 months	25%	0.33	42%	−0.14	−0.47
42 months	23%	0.39	42%	−0.14	−0.53
48 months	21%	0.44	33%	0.10	−0.33
54 months	20%	0.47			
60 months	19%	0.52			

Table 2. Patient characteristics and number of treatment arms included in the meta-analysis

Factors analysed	Mean percentage of patients	Number of treatment groups evaluated
FIGO		
IIb/III	73	66
IV	27	66
Histological type		53
serous	62	
mucinous	7	
endometrioid	7	
clear cell	1	
undifferentiated	13	
unclassified	4	
missing	6	
Histological grade		61
well differentiated	13	
moderately differentiated	30	
poorly differentiated	51	
Residual tumour		
less than 2 cm	27	61
more than 2 cm	67	61
missing	6	
Response to therapy		
Clinical		
(denominator: all patients registered)	49	66
(denominator: evaluable pts only)	57	66
Complete surgical remission	20	26
Performance status		
ECOG 0–1	81	19
ECOG 2–4	19	19
Chemotherapy regimens with:		
cisplatin		33
Adriamycin®		26
cyclophosphamide intravenously		27
cyclophosphamide orally		18
hexamethylmelamine		15
5-fluorouracil		9
methotrexate		8
melphalan		19
chlorambucil		5
C. parvum		2
leucovorin		1
treosulfan		3

percentages in Table 2. The mean percentage figures are based on the average of the patient numbers from the original articles.

We analysed 38 articles [1, 11–47] with 66 treatment groups containing a total number of 3443 patients. Histological type and grade were not registered in six arms. Survival curves were registered in 59 cases. Fifteen curves described a 60 month time period, two curves a time period of 54 months, eight curves 48 months, seven curves 42 months, 16 curves 36 months, five curves 30 months, and six curves described a 24 month period. All studies provided a median survival.

Relationship between survival and patient characterisics

Correlations of median survival, overall survival (measured by the LRR) and patient characteristics are shown in Table 3. Using median survival as an end-point, we found a significant positive correlation between median survival and FIGO stage, residual tumour less than 2 cm, regimens including cisplatin or doxorobicin, the complete remission rate and overall response. Out of the 26 treatment regimens using doxorubicin in the combination, 19 used cisplatin simultaneously. The LRR was significantly correlated with FIGO stage II/III, a good performance status, residual tumour less than

Table 3. Correlations between median survival, LLR, response and patient characteristics in a total of 38 articles

	Median survival		Log (relative risk)		Overall response (all patients)		Overall response (evaluable patients)		Surgical complete remission rate	
	PCC	*P*-value	PCC	*P*-value	PCC	*P*-value	PCC	*P*-value	PCC	*P*-value
FIGO stage IIb/III	0.35	(0.00)	−0.35	(0.00)	−0.29	(0.41)	0.04	(0.38)	0.09	(0.32)
Performance status 0, 1	0.28	(0.13)	−0.42	(0.05)	0.19	(0.22)	0.40	(0.04)	0.19	(0.13)
Mean age	−0.03	(0.81)	NC		−0.39	(0.00)	NC		−0.01	(0.96)
Histological type:										
serous	0.12	(0.20)	−0.18	(0.11)	0.14	(0.15)	−0.26	(0.43)	−0.44	(0.02)
mucinous	−0.12	(0.20)	0.23	(0.06)	−0.15	(0.14)	−0.10	(0.23)	−0.38	(0.44)
endometrioid	0.09	(0.25)	−0.09	(0.27)	−0.34	(0.00)	−0.19	(0.08)	0.28	(0.11)
clear cell	0.03	(0.41)	0.08	(0.29)	0.06	(0.33)	0.08	(0.28)	−0.02	(0.47)
undifferentiated	0.14	(0.16)	0.06	(0.33)	0.17	(0.11)	0.19	(0.09)	0.22	(0.16)
Histological grade:										
well differentiated	−0.02	(0.45)	−0.14	(0.15)	−0.08	(0.26)	−0.02	(0.44)	−0.39	(0.04)
moderately differentiated	0.06	(0.33)	0.04	(0.38)	−0.10	(0.22)	−0.11	(0.20)	0.15	(0.25)
poorly differentiated	−0.01	(0.46)	−0.01	(0.48)	0.20	(0.06)	0.14	(0.13)	−0.28	(0.11)
Residual tumour less than 2 cm	0.50	(0.00)	−0.44	(0.00)	−0.16	(0.11)	0.06	(0.31)	0.35	(0.04)
Cisplatin containing regimens	0.54	(0.00)	−0.52	(0.00)	0.23	(0.03)	0.43	(0.00)	0.30	(0.07)
Doxorubicin containing regimens	0.32	(0.01)	−0.37	(0.00)	0.15	(0.12)	0.35	(0.00)	0.09	(0.33)
Surgical complete remission rate	0.46	(0.01)	−0.45	(0.02)	0.31	(0.06)	0.26	(0.10)	**	
Overall response (all patients entered)	0.15	(0.12)	−0.24	(0.03)	**		0.81	(0.00)	0.31	(0.06)
Overall response (all patients evaluable)	0.25	(0.02)	−0.36	(0.00)	0.81	(0.00)	**		0.26	(0.10)
Median survival	**		−0.83	(0.00)	0.15	(0.12)	0.25	(0.02)	0.46	(0.01)
LRR	−0.83	(0.00)	**		−2.24	(0.03)	−0.36	(0.00)	−0.45	(0.02)

Abbreviations used: PCC = Pearson correlation coefficient; NC = not computed.

2 cm, cisplatin or doxorubicin containing regimens, the surgical complete remission rate and overall response. Note that a negative correlation means an improved overall survival because of the way the LRR is defined. For other prognostic factors the correlation was less obvious. No correlations were found for histological type and grade.

As a result of the multiple regression the use of cisplatin was found to be a factor that predicts independently of other variables a prolonged median survival ($P = 0.011$) and LRR ($P = 0.005$). A similar prolongation of survival was found in studies which had a large proportion of patients with small tumour masses in the patient material (*P* value with median survival as an objective: 0.011, with the LRR as an objective: 0.04).

Relationship between survival and response

The median survival and overall survival (measured by the LRR) was significantly prolonged in studies with a high complete surgical remission rate. This is shown by the significant correlations between the complete surgical response rate, median survival and LRR.

Clinical overall response rate including all entered patients showed no correlation with median survival. However, there was a positive correlation between clinical response as a percentage of the number of evaluable patients and the median survival. The LRR correlated with both overall response rates.

Relationship between registered variables

The relations between a number of prognostic factors are summarized in Table 4. We found a strong positive correlation (0.46) between the use of cisplatin containing regimens and the percentage of patients entered in a study with a residual tumour of less than 2 cm. A small tumour residuum was also positively correlated (+0.32) with a FIGO stage IIb/III.

Table 4. Relationships between different prognostic variables

	FIGO stage IIb/III	Residual tumour less than 2 cm	Performance status 0, 1	Toxicity related deaths	Cisplatin containing regimens
FIGO stage IIb/III	**				
Residual tumour less than 2 cm	$P = 0.006$	**			
Performance status 0, 1	NS	NS	**		
Toxicity related deaths	NS	$P = 0.003$	$P = 0.025$	**	
Cisplatin containing regimens	NS	$P = 0.000$	NS	NS	**

Statistical test: Pearson correlation coefficient, NS = not significant. The *P*-values are based on the correlations beween the percentages of the total number of patients in each treatment, not on absolute patient numbers.

A good performance status showed a strong negative correlation (−0.46) with toxicity related deaths, indicating that by entering more patients with a poor performance status the risk for toxic deaths increases. In contrast a positive correlation (0.35) was found between the percentage of toxic related deaths and a small tumour residuum prior to treatment. No differences were noted in the patient characteristics and treatment results between North America and Europe.

DISCUSSION

In order to evaluate the relation of prognostic factors and treatment on the overall long term survival, we introduced the log (relative risk), LRR as a long term survival figure. Median survival usually represents a 2 year time period while LRR comprises a complete survival curve over a time period of 3–5 years. Comparing the correlation of prognostic variables with the median survival and the LRR, it is shown that the LRR is more sensitive and also selects performance status as a factor predicting survival. Within the categories of histological grade the LRR shows that in studies including a large proportion of well differentiated tumours long term survival is often improved. This trend is not visible when the median survival is used as an endpoint. The recognition of the differentiation grade as a predictor of long term survival is confirmed in a multivariate analysis of the long term results from the Netherlands Joint Study Group [48].

The choice of chemotherapy, FIGO stage and the residual tumour prior to treatment predict both the duration of median survival and the LRR. Furthermore this study confirms the importance of the performance status in predicting long term results as was reported by the Netherlands Joint Study Group. Although performance status is important in predicting long term survival, as measured by the LRR, only 19 articles included the performance status in their publication. Future studies should always mention the performance status as a prognostic factor.

The prognostic factors predicting survival were not the same factors predicting overall response to chemotherapy. Undifferentiated tumours were more likely to respond. Because this factor did not predict survival these responses are probably of short duration. It is not clear why younger patients and endometrioid tumours are less likely to respond. This finding has not been reported by other investigators. As expected from data in the literature the use of cisplatin enhances the response rates and a small tumour prior to treatment predicts a better chance of achieving a complete remission at second-look [49, 50].

We demonstrated a strong correlation between survival and cisplatin or doxorubicin containing regimens. However, the relation between the use of doxorubicin and an improved survival is probably not relevant because in most cases cisplatin was also used in combination. This was confirmed by the results of the multivariate analyses where doxorubicin did not come out as an independent factor but cisplatin did. Although the use of cisplatin in the multivariate analyses predicted improved survival, it must be noted that the good results in studies using this drug may be influenced by the favourable patient characteristics in these studies. We found a positive correlation between the use of cisplatin and the percentage of patients with a residual tumour of less than 2 cm included in the study material (see Table 4). This indicates that patients with a more favourable prognosis are entered in trials using this drug.

It was a remarkable finding that patients with a good performance status were less likely to die as a result of toxicity. The inclusion of a large proportion of patients with small tumour residuals correlated with more toxic deaths. This may indicate that patients with small tumours and a potentially good prognosis received more aggressive treatment and probably higher dosages of the prescribed chemo-

therapy. This may be a factor that is of importance in dose–intensity studies as performed by Levin and Hryniuk [51].

Inconsistency in the description of patient characteristics and trial data was a major problem in collecting the data for this meta-analysis. Differences were noted in the description of residual tumour mass, histological grade, toxicity and response definition. Despite these problems this study emphasizes the use of cisplatin as a major drug in the treatment of ovarian cancer, the importance of tumour residuum and performance status as prognostic factors. The data in our study show how the selection of patient material can influence study outcome in terms of survival. Therefore the results of studies in ovarian cancer cannot be compared with each other without taking into account the patients entered into the study.

We conclude that the use of LRR as an overall long term survival figure is a meaningful addition in evaluating long term treatment results in a meta-analysis and can be used in other tumour types as well for the detection of relevant prognostic factors predicting long term survival.

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