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Original Paper

Response to Chemotherapy has Predictive Value for Further Survival of Patients with Advanced Non-small Cell Lung Cancer: 10 Years Experience of the European Lung Cancer Working Party

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The aim of this study was the assessment of the predictive value for survival of an antitumoral response to three courses of chemotherapy in association with various pretreatment characteristics in patients with non-resectable non-small cell lung cancer treated by cisplatin- (or carboplatin)-based combination regimens. Patients considered for this study were eligible patients with advanced non-small cell lung cancer registered in one of the seven trials conducted by the European Lung Cancer Working Party from December 1980 to August 1991. All these trials tested chemotherapy regimens with platinum derivatives (cisplatin and/or carboplatin). In this population of 1052 eligible patients, 752 were assessed in this analysis. Data were prospectively collected on 23 pretherapeutic variables and objective response after three chemotherapy cycles. The predictive value of response to chemotherapy on survival (measured from the time of response assessment i.e. 12 weeks after registration in the trial) was studied by univariate analysis as well as by multivariate methods (adjustment of the impact of several covariates simultaneously on the dependent variable) with adjustment for the pretreatment prognostic variables. After three cycles of chemotherapy, the global estimated median survival time was 24 weeks with a 95% confidence interval of 22–25 weeks. By univariate analysis, we identified an objective response to chemotherapy as a highly significant discriminant marker ($P < 0.0001$) for further survival with estimated median survival times of 41 weeks (95% CI: 38–46) and 19 weeks (95% CI: 17–20), respectively, for the responding and non-responding patients. In a Cox regression model fitted to the data using a forward stepwise procedure, this variable was the first selected explanatory variable. Its effect was adjusted by the introduction in the model of initial disease extent, Karnofsky performance status, serum calcium level and white blood cell count. These results were consistent with those obtained by application of recursive partitioning and amalgamation algorithms (RECPAM) which led to a classification of the patients into three homogeneous subgroups. Our results, using a classical Cox regression model consistent with those highlighted by application of a RECPAM analysis, found an objective response to chemotherapy to be a predominant predictive factor for further survival, although it did not allow any conclusion about a causal relationship. The RECPAM results led to a classification of the patients into three subgroups which needs to be validated in other series.

Key words: advanced NSCLC, objective response to chemotherapy, survival, prognostic factors
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INTRODUCTION

PROGNOSIS OF patients with unresectable non-small cell lung cancer (NSCLC) is poor, with little hope of cure [1]. Chest irradiation has mainly palliative effects [2] and there has been a considerable debate over the two last decades on the role of chemotherapy in the therapeutic management of those patients. However, there is now enough evidence that survival is improved, even though the benefit is small, by the use of cisplatin-based regimens [3]. The magnitude of the benefit has been recently estimated by four meta-analyses [4–7] based on published results or individual patient data.

In view of these results and considering that we have already shown [8] that obtaining, with chemotherapy, an antitumoral response has a favourable impact on long-term survival (more than 2 years), we assessed how prediction of the prognosis of individual patients could be improved by adding, to the pretherapeutic prognostic factors that we identified [9], the potential discriminant value of response to chemotherapy. The knowledge of this revised prognosis could be useful for individual patient information, but also for selecting the subgroup of patients with the best long-term survival chance in order to investigate the value of complementary therapy.

The purpose of this report was to analyse retrospectively the value of response to chemotherapy alone and in combination with pretherapeutic factors on the postevaluation survival of patients registered from 1980 to 1991 in the clinical trials of the European Lung Cancer Working Party (ELCWP).

PATIENTS AND METHODS

Patients and trials

The patients considered for our analysis were eligible patients with NSCLC treated by chemotherapy (combined in a few cases with radiotherapy) and registered in a clinical trial of the ELCWP from December 1980 to August 1991. These phase II or III trials [10–16] have been individually published and are summarised in a previous publication [9]. Eligibility criteria included the existence of pathologically proven unresectable NSCLC with the presence of an evaluable or measurable lesion in a patient with a Karnofsky performance status of at least 60. Prior chemotherapy was forbidden in 4 trials [11, 13, 14, 16]. Patients with both limited disease (LD = stages I–III) or metastatic disease (MD = stage IV) were eligible except in two trials [11, 16]. Age had to be < 75 years, except in one trial [15] where there was no age limit. There should be no history of other malignancies except in two trials [15, 16] (where a 5-year tumour-free period was, however, required). Presence of brain metastases was a criterium of exclusion except in the last two trials [15, 16]. In each trial, adequate renal, hepatic and haematological functions were required, as well as no recent myocardial infarction and no active cardiac or infectious disease.

Minimal staging assessment before treatment included clinical examination, ECG, chest X-rays, chest CT-scan, bronchoscopy, bone scintigraphy with X-rays or CT-scan of suspected areas, isotopic scan, CT-scan and/or echography of liver (and possibly adrenals), isotopic scan or CT-scan of the brain, laboratory studies including haematological, renal and hepatic tests. Staging was repeated for response evaluation with the same assessment after two [10, 12, 15] or three [11, 13, 14, 16] courses of chemotherapy. Antitumoral response was originally evaluated during regular meetings of the Group by at least three independent observers, using the WHO criteria with a classification into complete response, partial response, stable disease, progressive disease, early death and non-evaluable response. However, for the purpose of the present analysis, the response variable was considered binary: objective antitumoral response or failure. As the complete response rate was very low, we did not feel it was useful to distinguish between complete and partial response.

Statistical methodology

The statistical analysis was performed using the software SPSS/PC [17], BMDP [18] as well as own written programs (available on request to the corresponding author). The dependent variable that we studied was survival duration defined as the time elapsed from the time when response to chemotherapy was assessed until death or the date of the last follow-up (31 August 1992). However, precise timing of the staging for response assessment was not available and we arbitrarily considered that response was evaluated for all the patients after 12 weeks (the longest delay since therapy initiation for all the trials included in the analysis) and used this delay as a landmark in order to minimise the methodological problems related with the existence of a guaranteed survival time among the responders and to obtain a statistically correct analysis of survival according to tumour response [19]. Patients having died within 12 weeks after therapy initiation were therefore excluded from the analysis. It was impossible to apply the technique to reassess continuously the status response of a patient because the date of first observation of a response was unknown. Incorporation in the analysis of the pretreatment independent variables was performed with a dichotomisation of the values of these variables. Namely, the biological values were dichotomised into normal and abnormal values according to standard laboratory norms. Metastatic involvement was considered separately at different sites (lung, liver, bones, adrenals, brain, skin). The 23 pretherapeutic factors which were considered are displayed in Table 1.

For univariate analysis, survival distributions were estimated by the method of Kaplan and Meier and compared according to one factor by the log-rank test [20]. The survival duration was further estimated by fitting the data with a Cox regression model after verification of the proportional hazards assumption by looking at the graphical display of the logarithms of the cumulative hazards against time [21]. The explanatory variables were selected by using a stepwise forward procedure with an enter limit fixed as a significance probability of 0.05. Confidence intervals for relative risks were calculated.

Finally, in addition to the Cox regression analysis, a recursive partitioning algorithm followed by an amalgamation algorithm (RECPAM) [22] was applied in order to identify subgroups of patients, who were homogeneous for outcome, by constructing a tree structure. Indeed, such algorithms have the advantage of a more intuitive construction of a classification than with the best Cox fitted model (in that case, it is necessary to categorise the hazards function using some cut-offs) with a quite arbitrary choice for their number and their values but have some disadvantages, such as to be less sensitive in the detection of additional factors (due to its sequential approach) and to lack usefulness for estimation purposes. Results obtained by the classical approach, which is still the reference and more accepted method, are also reported in order to be able to compare both techniques. The root of the

Table 1. *Descriptive results*

Variable*	Categories	Numbers of evaluable patients
Sex	male/female/missing	674/78/0
Age (years)	< 60 y/≥ 60 y/missing	330/422/0
Loss of body weight	< 5%/≥ 5%/missing	408/263/81
Histology	squamous cell adenocarcinoma other missing	431 230 91 0
Prior therapy	no/yes/missing	665/85/2
Karnofsky performance index	≤ 70/> 70/missing	274/478/0
Disease extent	limited/disseminated/missing	292/460/0
Type of lesion	evaluable/measurable/missing	375/375/2
White blood cell count	$\leq 10 \times 10^3/mm^3$ (NL)/> NL/missing	461/281/10
Neutrophil count	≤ 75%/> 75%/missing	484/239/29
Platelet count	$\leq 440 \times 10^3/mm^3$ (NL)/ > NL/missing	533/207/12
Haemoglobinaemia	inside [12–18 g/100 ml] outside [12–18 g/100 ml] missing	575 165 12
Serum alkaline phosphatases	≤ 110 mU/ml (NL)/ > NL/missing	267/434/51
Bilirubinaemia	≤ 1 mg/100 ml (NL)/ > NL/missing	657/15/80
Creatininaemia	≤ 1 mg/100 ml (NL)/ > NL/missing	530/192/30
Serum lactate dehydrogenase	≤ 200 mU/ml (NL)/ > NL/missing	152/284/316
Calcaemia	≤ 10.3 mg/100 ml (NL)/ > NL/missing	480/28/244
Lung metastases	no/yes/missing doubtful	566/110/76 0
Liver metastases	no/yes/missing doubtful	430/105/201 16
Bone metastases	no/yes/missing doubtful	348/168/194 42
Adrenal metastases	no/yes/missing doubtful	442/69/228 13
Brain metastases	no/yes/missing doubtful	469/42/234 7
Skin metastases	no/yes/missing doubtful	520/13/219 0

*Each variable was measured before therapy. NL, normal.

tree was defined as the whole population. At each step of the recursive partitioning algorithm, a splitting was performed according to a dissimilarity measure, calculated on the values of the covariates, and the subgroups of patients obtained after a splitting were called nodes of the tree. At each node, the dissimilarity measure used was the value of the log-rank statistic of the hypothesis that the survival curves, obtained when stratifying the subgroup of patients in this node according to one covariate, differed versus the hypothesis that they were the same. As the covariates were all categorised, the calculation of this dissimilarity measure was always feasible. The best split for the node was the one corresponding to the log-rank statistic having the smallest significance level (obtained from an asymptotic chi-square distribution). For this calculation, missing data were ignored. If this smallest significance level, adjusted for multiple comparisons by an improved Bonferroni method within each interior node [23], was less than 0.05, the split was performed but only if this subdivision led to nodes including more than 20 patients. Otherwise, construction of the partition stopped and the node was called a terminal node. When further splitting was impossible, the terminal nodes were clustered following the amalgamation algorithm: at each step, the log-rank statistic testing the hypothesis that the survival curves of two nodes differed versus the hypothesis that they were the same was calculated and the one having the greatest significance level was searched; if this maximal significance level was greater than 0.05, the two corresponding nodes were joined to form one new terminal node. The same procedure was then applied on the set of new terminal nodes. This recursive amalgamation algorithm was stopped when no significance level above 0.05 was found.

All these techniques were applied to covariates measured before treatment, together with the response status. All

the significance probabilities that we calculated were two-tailed.

RESULTS

We collected pretherapeutic data for 1052 patients included in a common database, all registered in the trials before 31 August 1991. The date of reference for the survival analysis was 31 August 1992. After the landmark of 12 weeks, 810 patients were still alive. Among those patients, 246 (30%, 95% CI: 27–34) were assessed as responders, 506 failed to respond to three courses of chemotherapy and 58 were non-evaluable (25 for treatment refusal, 18 for major protocol violation and 15 for incomplete or refusal of clinical assessment); leaving 752 patients assessable for the present analysis.

We reached, for this cohort, a median for further follow-up of 265 weeks (range 1–616 weeks); at the date of analysis, 700 patients were dead (93%), 28 still alive (4%) and 24 lost to follow-up (3%). Survival times are given from the landmark, i.e. starting 12 weeks after registration in the trial.

Overall, by estimating the survival distribution by the non-parametric method of Kaplan and Meier, we obtained a median survival time estimate of 24 weeks with a 95% confidence interval of 22–25 weeks. The actuarial 2- and 5-year survival rates were, respectively, 6% and 2%.

Comparison of the survival distributions of the responders and the non-responders was highly significant in favour of the responder group. Their estimated median survival time was 41 weeks (95% CI: 38–46) compared with only 19 weeks (95% CI: 17–20) for patients with treatment failure. The survival curves are presented in Figure 1. To adjust the effect of response according to pretherapeutic prognostic factors, the survival duration was further modelled with a multivariate Cox regression analysis with the hypothesis of proportional hazard rates. The first set of variables retained, on the basis of univariate log-rank tests, for potential inclusion in the model, were the following: sex, age, loss of weight, existence of prior therapy, Karnofsky performance status, disease extent, white blood cell, neutrophil and platelet counts, haemoglobinaemia and response to chemotherapy status. Serum calcium level and presence of lung, liver, bone, adrenal, brain or skin metastases should have been retained but were excluded due to high levels of missing data (all the variables relative to metastatic site are well summarised by the disease extent variable). All these variables were dichotomised as explained above. The coding value 1 was systematically assigned to the first category listed in Table 1 and the coding value 2 assigned to the second one. Using a forward stepwise procedure for selection of the model, objective response to chemotherapy was the first variable entered in the model followed by disease extent, Karnofsky performance status, age and white blood cell count. Estimated coefficients of the model with estimated instantaneous relative risks of death with confidence intervals are presented in Table 2. For the construction of this model, data relative to 655 patients were used (87% of the whole population). The model remains stable when excluding weight loss on the basis of 737 patients (98% of the patients).

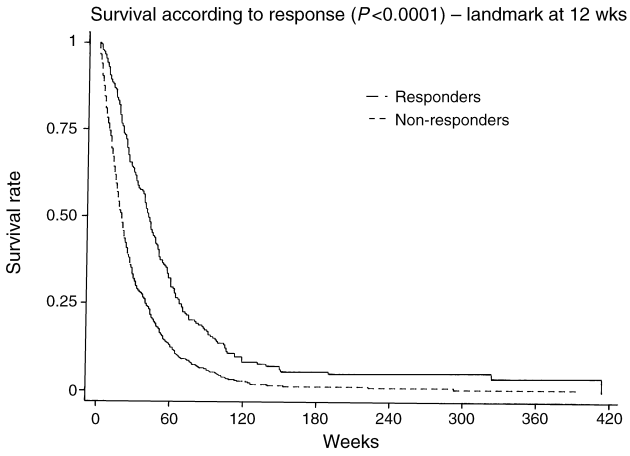

Figure 1. Estimated survival curves according to response status.

We applied a recursive partitioning algorithm to the survival data, using the same covariates as for Cox's regression model and constructed a tree shown in Figure 2. Terminal nodes of the partitioning algorithm are represented by squares, final clusters after application of the amalgamation algorithm by hexagons and the other nodes by circles. The

Table 2. Best fitted Cox multivariate regression model

Variable	Coefficient	Standard deviation	RR (CI at 95%)	*P*
Objective response yes no	0.79	0.09	2.20 (1.85–2.61)	< 0.0001
Disease extent limited disseminated	0.42	0.08	1.53 (1.29–1.81)	< 0.0001
Karnofsky PS ≤ 70 ≥ 80	–0.33	0.09	0.72 (0.61–0.85)	0.0002
White blood cell count normal abnormal	0.19	0.09	1.21 (1.02–1.43)	0.04
Age ≤ 60 years > 60 years	0.16	0.08	1.17 (1.00–1.38)	0.05

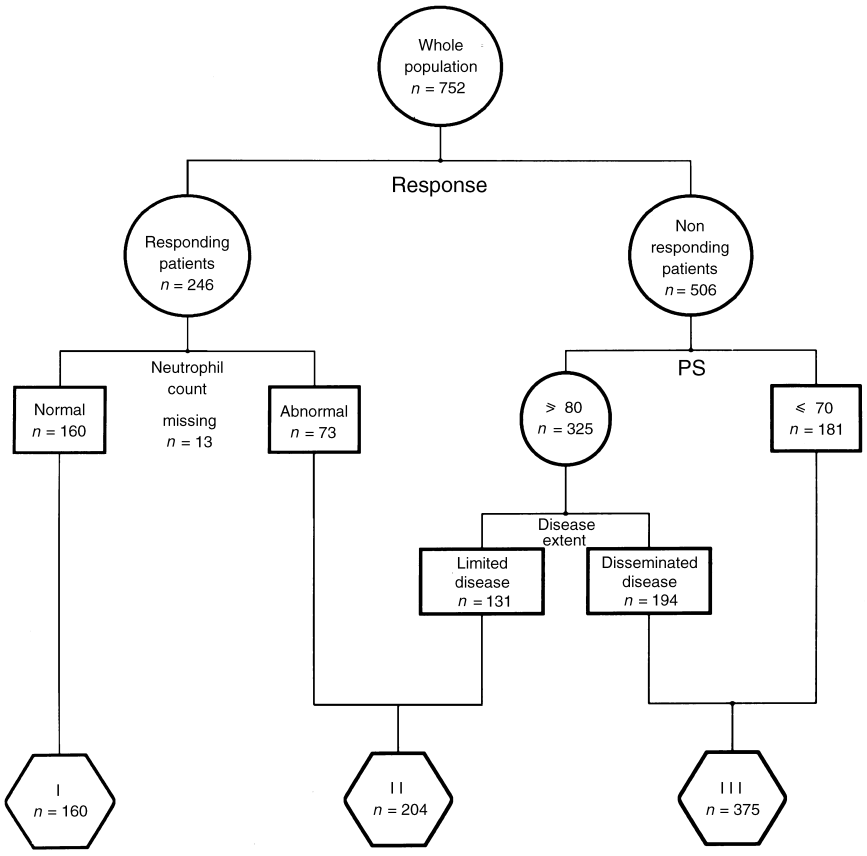

Figure 2. RECPAM tree.

number written in the node is the number of patients belonging to this node. After a split, the subgroup of patients with the best survival is the one represented by the left node. The first variable which divided the whole population was objective response to chemotherapy. For the responding patients, the next most important variable related to survival was the neutrophil count status leading to two final subsets: responding patients with or without a neutrophil count in the normal range. The non-responding patients were subdivided at the second step according to their Karnofsky performance status and those with a good index were then discriminated according to their initial disease extent, leading to three more final nodes. After application of an amalgamation algorithm on the total five final subsets, we identified three subgroups of patients heterogeneous for survival. The best one (group I) included responding patients with a normal neutrophil count, the intermediate one (group II) consisted of responding patients with an abnormal neutrophil count and of non-responding patients with a high Karnofsky index and limited disease. The third group (group III) with the poorest survival included non-responding patients with a poor Karnofsky index. The estimated median survival times for these three heterogeneous subgroups were, with their 95% confidence intervals in parentheses: 47 weeks (41–53) for group I, 31 weeks (26–37) for group II, and 16 weeks (14–17) for group III. Their estimated survival curves are shown in Figure 3.

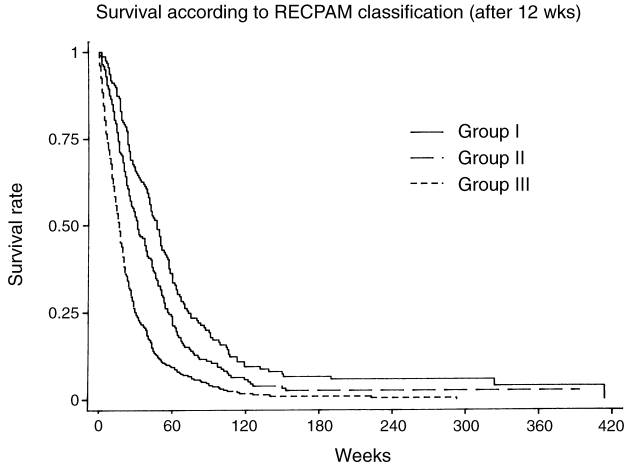

Figure 3. Estimated survival curves for the three homogeneous subgroups identified by the RECPAM analysis.

We also considered the 58 non-evaluable patients, assimilating them as patients not responding to chemotherapy. We obtained similar results (data not shown). To assess the stability of our results, we also looked at a potential time effect (including variation in the administered chemotherapy regimens and/or in the patient population) by constructing a categorical variable with three levels: registration before January 1985, registration between January 1985 and May 1989, registration after May 1989. The first category corresponds to trials [10–12], the second to trials [13, 14] and the last to trials [15, 16]. This variable had no impact on our results in either univariate or multivariate analysis (data not shown).

DISCUSSION

During the last decade, there has been considerable debate about the usefulness of chemotherapy in prolonging survival of patients with advanced NSCLC. There is now convincing data [4–7] showing that chemotherapy brings a definite survival advantage, even through the magnitude of the benefit remains disappointing. Therefore, it is of interest to know whether, by evaluating response to chemotherapy, we can identify patients who will enjoy longer survival, although the predictive value of this variable cannot constitute proof of chemotherapy efficacy. Knowledge of this predictive variable seems to us extremely valuable on an individual basis so that the clinician can inform the patients about their chances of prolonged survival once objective response is documented. This information could also be useful in designing trials for responding patients; it is perhaps a valuable argument to look for regimens increasing response rates, even though actual trial results generally fail to demonstrate survival benefit when response rate is improved. Our results should also encourage research on the 'optimal' definition of response: our present criteria are based on arbitrary reductions of tumour area and could probably be improved. The reason why responding patients receiving more chemotherapy courses show a better prognosis remains unknown and raises the question of clinical benefit obtained with treatment continuation, but the answer can only be obtained from a randomised trial.

We found a highly statistically significant value for response on survival after evaluation, with a median survival duration estimated to be more than double for responding patients. At that time, this variable provides more discriminant information than any of the pretherapeutic prognostic factors we identified. When adjusting the effect of this variable using a tree structure through a RECPAM analysis, we could further classify the patients with a 3-fold difference in the estimated median durations between the subgroups of patients with the poorest and the best survival. As this difference was calculated on the same sample as the one used to construct the classification, it is probably an overestimation and needs to be validated in another series.

To our knowledge, such a study has rarely been conducted, but our findings were consistent with those of O'Connell [24] using a similar landmark at 10 weeks. Sorensen [25], on a smaller patient population, with a landmark at 16 weeks, failed to show a survival benefit for responders; these conflicting results could be related to a lack of statistical power or could be explained by a possible fall in the magnitude of the benefit attributable to chemotherapy response as time passes. This assumption is confirmed by one [5] of the meta-analyses evaluating polychemotherapy versus best supportive care. Indeed, a beneficial effect of polychemotherapy after 3 and 6 months was found, but the reduction in mortality observed in the polychemotherapy arms decreased after 9, 12 and 18 months to become non-significant. Chemotherapy regimens could also explain the inconsistency of our results with those of Sorensen [25] Indeed, in this latter study, patients were treated by vindesine alone or with a combination of cyclophosphamide, lomustine, methotrexate with or without vindesine, while our patients all received a regimen based on cisplatin (or carboplatin) which is the only drug so far shown to be associated with a survival benefit in advanced NSCLC.

Our study gave white blood cell count or the neutrophil count (which are two variables closely related) a role in the models of the survival distributions and in the construction of the classification; this is an original result which needs confirmation since we could not find in the literature any prognostic study of this variable; the relative importance of these counts in addition to the traditional prognostic factors (Karnofsky index and disease extent) merits further investigations.

Some limitations of our study have to be outlined. Firstly, due to the retrospective nature of our analysis, we have associated one post-therapeutic variable with factors measured before therapy initiation without taking into account the evolution of these parameters. It would be interesting to adjust the effect of response to chemotherapy with the prognostic factors re-evaluated at the moment of response assessment in order to see if the high discriminant value of response is maintained. Secondly, we had to deal with missing data and remove some variables, due to lack of data, from the multivariate analyses, creating potential problems of generalisation; however, the sensitivity analyses we performed did not show consistency problems. We also omitted from the analyses the patients who did not survive 12 weeks in order to eliminate the bias due to a guaranteed survival time for the responders, but we failed to identify specific characteristics for these patients (data not shown). Staging examination for response assessment has probably not changed enough during the study period to have induced a significant bias and timing for response evaluation could not greatly influence our results since we have shown in the individual papers that early response status did not vary much from best response status. Furthermore, we used the classical criterium of a 50% decrease of the tumour load to define an objective reponse, but we do not have data to be sure that this cut-off correctly reflects the most biologically significant size reduction of the tumour. Some patients, non-evaluable for response to chemotherapy, were omitted from the primary analyses, but without any major bias introduction because results remained stable when new survival models were constructed, assimilating them as patients having treatment failure. The stability of our findings is encouraging for the validity of the identified prognostic factors as well as the consistent results obtained with the complementary approaches of the two techniques that we used for data analysis: the tree approach for construction of the classification and the Cox regression for estimation of the effects of the important variables.

Finally, some heterogeneity in patients' selection criteria and changes in the chemotherapy regimens have to be noted. As the primary purpose of our analysis was to look at the predictive value of objective response on survival in the context of a multivariate adjustment for other prognostic factors rather than precise estimation of the survival duration of a highly selected patient subgroup, we were interested in the analysis of the whole group of patients that we considered homogeneous enough to be treated in the same way. Therefore, we did not perform any exclusion. Moreover, as we did not see any time effect on our results, we do not think that heterogeneity in the trials prevents interpretation of our findings.

In conclusion, in spite of the methodological problems related to the introduction of response to chemotherapy as a variable in survival comparisons, our results clearly show that obtaining an objective response is the strongest marker of prolonged survival and suggests that its prognostic

information could be significantly improved by pre-therapeutic neutrophil count, Karnofsky performance and disease extent. This information is valuable for individual patient's information, but perhaps also for the investigation and elaboration of consolidation treatments for responding chemotherapy patients.

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