(Please see File S1). A total of 10,262 patients had been allocated randomly to 110 chemotherapy arms.

Study Characteristics

Table 1 lists the baseline characteristics of the trials. Trials were initiated between 1980 and 2006. The number of randomized patients and the proportion of patients with good PS increased over time (13.9 patient increase/year, $P<0.001$; and 1.32% increase/year, $P<0.001$, respectively; Figures 2A and 2B), whereas the proportion of male patients remained consistent (0.47% decrease/year, $P=0.114$; Figure 2C). In 19 trials that assigned PCI, it was planned that patients who achieved a complete response (CR) or CR/partial response (PR) after induction chemotherapy would receive PCI. Thirteen (25%) of the 52 phase III trials showed a statistically significantly difference in survival time. Of these, eight were in favor of the patient cohort that received the experimental therapy compared with the control group, while the remaining five were in favor of that in the control group.

Table 1. Characteristics of the 52 Randomized Trials.

Variable	Value
No. of trials	52
(No. of randomized patients in all trials 10262)	
No. of treatment arms	
2	47
3	4
4	1
Year of trial initiation	
Median (range)	1990 (1980–2006)
No. of randomized patients (%)	
<100	35
100–200	25
200–300	29
>300	11
Median (range)	158 (34–786)
Proportion of patients with good performance status† (%)	
<80	50
80–90	42
>90	8
Median percentage (range)	80 (35–100)
Male Patients (%)	
<80	54
80–90	35
>90	11
Median percentage (range)	75 (56–93)
Trials assigning PCI for those with CR or CR/PR to the initial chemotherapy	
Yes	37
No	63
Trials with a statistically significant difference in overall survival time (%)	
Yes	25
No	65
Not recorded	10

†Defined as a performance status of 0 or 1.
Abbreviations; PCI, prophylactic cranial irradiation; CR, complete response; PR, pertial response.
doi:10.1371/journal.pone.0007835.t001

Types of Chemotherapy Arms

There were 110 chemotherapy treatment arms in the 52 phase III trials (Table 2). Cisplatin-based regimens were the most frequently investigated. The PE regimen, currently considered as the standard treatment for patients with ED-SCLC, has increasingly been studied (Figure 1). As expected, the CAV alternating PE regimen was extensively examined in the 1980s, but this decreased in the 1990s.

Trends in Patient Survival

Data on patient survival were available from all 52 trials and 110 chemotherapy arms and analyzed by treatment arm. A scattergram of the two parameters (year of trial initiation and median survival time) revealed that the slope of the fitted line was 0.021, indicating a 0.021 month (0.63 day) increase in median survival time per year ($P=0.272$; Figure 3). Multiple regression analysis, adjusting for several confounding trial characteristics, also showed no significant association between the two parameters (regression coefficient for year of trial initiation $=0.011$, 95% confidence interval $=-0.36$–0.38, $P=0.950$; Table 3). In this setting, the proportion of patients with good PS was significantly associated with a favorable outcome. The multiple regression analysis also showed a significant influence of PCI setting on survival prolongation. This finding is partly supported by a recent report on the survival advantage of PCI in ED-SCLC patients who responded to initial chemotherapy [6].

Discussion

Our results demonstrate no significant improvement in patient outcomes over the years in phase III trials of systemic chemotherapy for ED-SCLC, with an increase of 0.021 months (0.63 days) per year (univariate analysis; $P=0.272$; Figure 3) confirmed in the multivariate model ($P=0.950$; Table 3). However, the proportion of patients with good PS and the trial design of assigning PCI for those with CR or CR/PR significantly influenced survival (Table 3).

The introduction of multiple drug regimens has been a great advance in the treatment of ED-SCLC; indeed, the CAV regimen yielded a survival time approximately twice as long as that of the single-agent therapy frequently used in the early 1970s [1,7]. However, the survival benefit from chemotherapy has reached somewhat of a plateau, even with the introduction of the PE regimen in recent clinical trials, as compared with the CAV regimen or CAV alternating PE [2,8,9,10]. In addition, most of newer antitumour agents introduced after PE (e.g., irinotecan and topotecan) failed to substantially prolong survival in the first-line setting over the standard PE regimen [11,12,13,14,15]. Thus, based on these findings, our main results demonstrate no significant improvement in survival since 1980. In contrast, a 1999 study showed a significant increase in overall survival time [3]. This difference in the time trend in overall survival is mainly attributable to differences in the study period (year of trial initiation: 1972–1994 vs. 1980–2006 in the earlier and present study, respectively; [3]).

In Figure 3, trials between 2000 and 2005 appeared to show extensive clustering with median survival time of around ten months. It would be attributable to some common characteristics among these trials, such as relatively uniformed chemotherapeutic regimens (cisplatin-based ones) and larger number of the registered patients. In contrast, there were other trial arms that yielded the

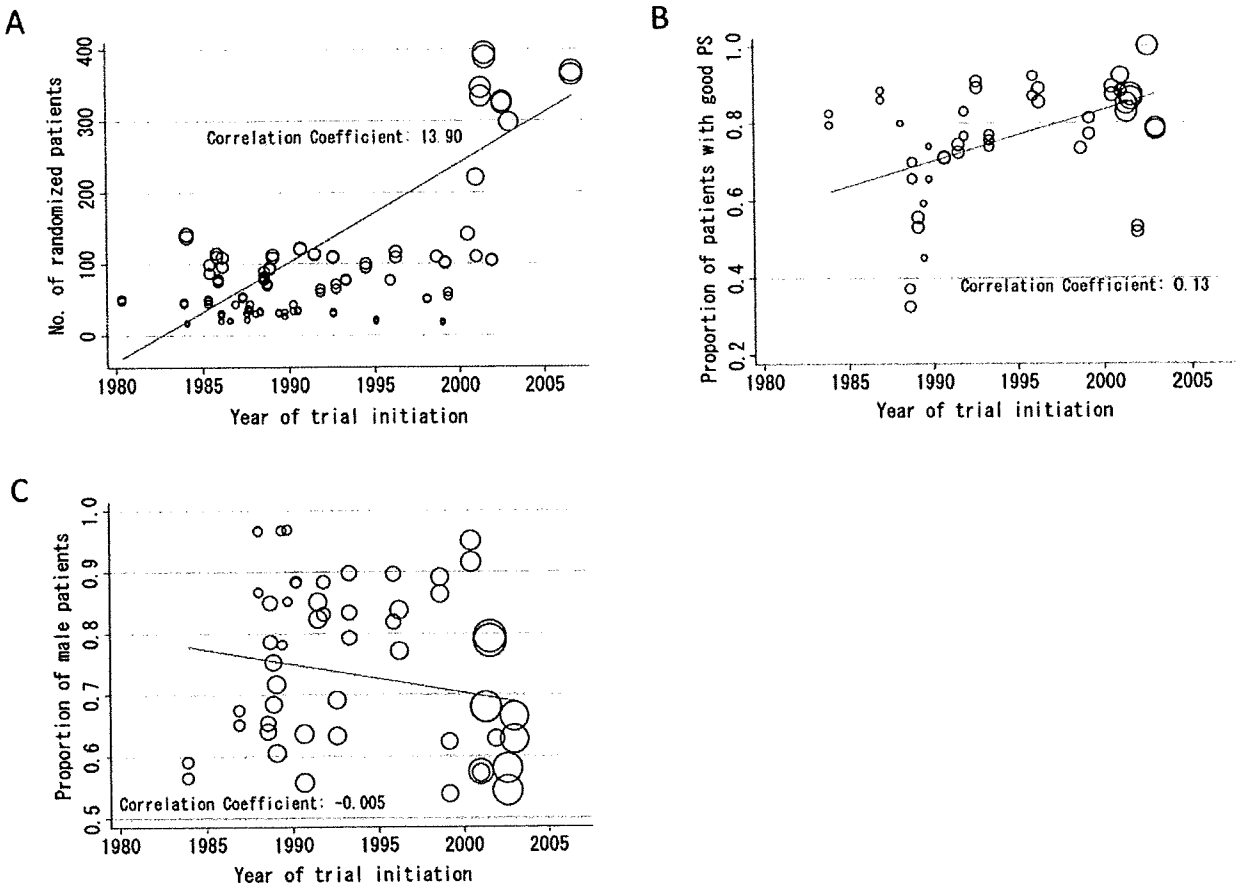

Figure 2. Trends in trial characteristics. These charts show the associations between year of trial initiation and number of randomized patients (A), proportion of patients with good PS (B), and proportion of male patients (C) in each trial. The size of solid circles represents data weighted on the basis of the number of randomized patients. Abbreviations: PS, performance status.
doi:10.1371/journal.pone.0007835.g002

longest versus shortest survival times (14–15 months versus 5–6 months). These included less number of the enrolled patients, which possibly resulted in a wide-range distribution in the Figure.

We investigated a similar issue previously [16], namely trends in prognosis over the years in chemo-naïve patients with advanced non-small cell lung cancer (NSCLC) enrolled in phase III trials.

Table 2. Types of Chemotherapy Arms and Treatment Outcomes (Per Treatment Arm).

Chemotherapy Arm	No. of Arms (%)	MST (range), months	
Total no. of arms	110	9.3	[4.9–14.5]
Platinum-based regimens	78 (70.9)	9.5	[4.9–14.5]
Cisplatin-based	64 (58.2)	9.6	[5.8–14.5]
CAV alternating PE	16 (14.5)	9.5	[5.8–14.5]
PE	16 (14.5)	9.4	[7.0–10.2]
Other Cisplatin-based	32 (29.1)	9.8	[6.7–12.8]
Nonplatinum regimens	32 (29.1)	8.5	[5.0–13.0]
CAV-based	10 (9.1)	9.1	[7.5–13.8]
Non-CAV-based combination therapy	19 (17.3)	8.2	[5.0–13.0]
Non-CAV-based monotherapy	3 (2.7)	8.3	[6.0–9.3]

Abbreviations: MST, median survival time; CAV, cyclophosphamide, doxorubicin, and vincristine; PE, cisplatin and etoposide.
doi:10.1371/journal.pone.0007835.t002

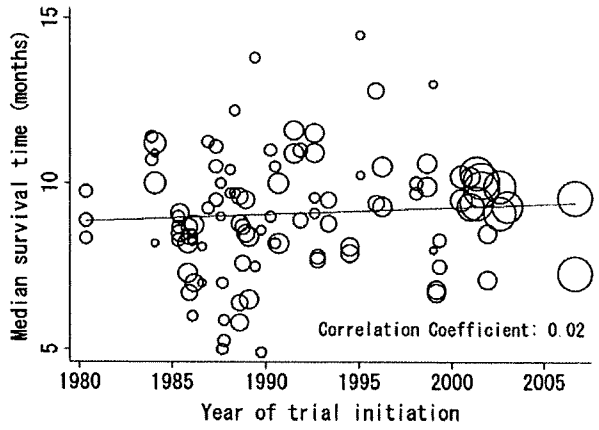

Figure 3. Relationship between year of trial initiation and median survival time. Analysis was weighted by the number of randomized patients. Each trial is represented by a circle; the size of each circle is proportional to the sample size of randomized patients in the given trial.
doi:10.1371/journal.pone.0007835.g003

Table 3. Multiple Stepwise Linear Regression Analysis of Overall Survival (Per Treatment Arm).

Factor	Regression Coefficient*	SE	P†
Year of trial initiation	Excluded		
Use of PE regimen (y or n)	Excluded		
Proportion of patients with good PS	6.65	1.30	<0.001
Proportion of male patients	Excluded		
Median age of patients	Excluded		
Design of the PCI setting (y or n)	2.14	0.742	0.009
Description of definition for ED (y or n)	Excluded		

*Threshold F values for entering and removing from the model were 0.05 and 0.10, respectively.
†$P<0.05$ was considered significant. This multivariate stepwise regression model excluded the factors "Year of trial initiation," "Use of PE regimen," "Proportion of male patients," "Median age of patients," and "Description of definition for ED" from the model.
Abbreviations: PE, cisplatin and etoposide; PS, performance status; PCI, prophilactic cranial irradiation; ED, extended disease.
doi:10.1371/journal.pone.0007835.t003

The analysis similarly revealed a very small increase in patient survival (3.61 days per year) but one that was statistically significant in the multiple regression model ($P<0.001$; ([16]). There may be several potential factors behind such differences in statistical results in SCLC and NSCLC settings. The most important is that new active agents such as taxanes appeared in the treatment of NSCLC [17,18] and few novel agents, including molecular-targeted agents, did in the treatment for SCLC [11,19,20,21] in these study periods. Another hypothesis is that advanced NSCLC might be more influenced than SCLC by lead time bias through early detection with improved imaging techniques, mainly because the growth rate of NSCLC is generally less rapid than that of SCLC throughout its natural history [22]. Progress in supportive care practices would lead to improvements in survival among patients with advanced NSCLC. Those with advanced NSCLC usually have less rapid disease progression and, thus, would likely benefit from its advancement. Finally, the statistical difference between our NSCLC and SCLC studies could have arisen from differences in sample size (number of trials), indicating that the current study may have lacked adequate power to accurately evaluate the association between the year of trial initiation and patient outcome.

The potential influence of second-line chemotherapy should also be considered in assessing the effect of first-line chemotherapy because it may contribute to recent improvements in survival [23]. The trials analyzed here rarely provided information about second-line treatment, and we can not assess its exact effect in this setting. There are few positive phase III trials of second-line treatments, and thus it is unlikely that such therapy can significantly confound patient prognosis after the initiation of first-line chemotherapy [24].

In conclusion, the results of our analysis suggest that, regardless of the reason, the survival of patients with ED-SCLC who were enrolled in phase III trials did not improve significantly over the years. Thus, the development of novel targets, newer agents, and comprehensive patient care will be essential in the future fight against lung cancer.

Supporting Information

File S1
Found at: doi:10.1371/journal.pone.0007835.s001 (0.05 MB DOC)

Author Contributions

Conceived and designed the experiments: KH. Performed the experiments: KH. Analyzed the data: IO KH. Wrote the paper: IO KH KK NO NT YF MT MT.

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original article

Annals of Oncology 20: 829–834, 2009
doi:10.1093/annonc/mdp020
Published online 16 February 2009

Association between incremental gains in the objective response rate and survival improvement in phase III trials of first-line chemotherapy for extensive disease small-cell lung cancer

K. Hotta*, K. Kiura, Y. Fujiwara, N. Takigawa, I. Oze, N. Ochi, M. Tabata & M. Tanimoto

Department of Respiratory Medicine, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama, Japan

Received 13 November 2008; revised 10 January 2009; accepted 13 January 2009

Background: The duration of, resources required for and cost of clinical trials could be reduced if a surrogate end point was to be used in place of survival. We assessed the extent to which the objective response rate (ORR) is predictive of mortality, how much difference in the ORR is needed to predict an obvious survival difference and what factors could affect the association between the two parameters during the first-line treatment of extensive disease (ED)-small-cell lung cancer (SCLC).

Methods: We used the ORRs and median survival times (MSTs) from 48 phase III trials of first-line chemotherapy involving 8779 randomised patients with ED-SCLC in a linear regression analysis. The MST difference was calculated as the difference in MST between the investigational and reference arms; the ORR difference was similarly defined.

Results: ORR difference between the treatment arms was modestly associated with the MST difference in the overall trials ($R^2 = 0.3314$). In contrast, the relationship was stronger among only trials in which prophylactic cranial irradiation was given to those having an objective response to the initial chemotherapy ($R^2 = 0.6279$). In this trial setting, large differences in ORR were needed to predict a survival advantage (1.2-day survival advantage per 2% increase in ORR).

Conclusions: In the first-line treatment of ED-SCLC, a favourable relationship was detected between the two parameters in the selected trial setting. Large ORR differences were needed to predict a survival benefit, clearly suggesting the need for new chemotherapeutic agents.

Key words: lung cancer, objective response, overall survival

introduction

Lung cancer is a leading cause of cancer-related death, and small-cell lung cancer (SCLC) accounts for ~15% of all lung cancer cases. SCLC is clinically categorised according to the disease extent as either limited disease (LD)- or extensive disease (ED)-SCLC. The standard first line of treatment of ED-SCLC is platinum-based chemotherapy with cisplatin–etoposide or cisplatin–irinotecan [1, 2]. The outcome, however, is unsatisfactory, with a median survival time (MST) of ~1 year, indicating the need for novel anticancer agents.

In developing new agents, the most important issue is whether they prolong survival. This is usually evaluated in phase III trials, in which the primary end point is traditionally overall survival (OS). Phase III trials, however, are both expensive and time consuming. Moreover, a recent review of all North American phase III randomised trials for patients with ED-SCLC conducted from 1972 to 1990 determined that only 5 (24%) of 21 trials found a significant, but small, survival advantage, with a survival difference ranging from 0.8 to 3.0 months in the experimental arm compared with the control arm [3]. Considering these findings, early and accurate screening of the agents to be investigated in phase III trials is essential.

As spontaneous cancer regression is a rare event, assuming that tumour regression after treatment is attributable entirely to a treatment effect is reasonable. For this reason, the objective response rate [ORR; complete response (CR) rate and partial response (PR) rate] has historically been considered a clear indicator of antitumour activity and a surrogate for clinical benefit [4]. The ORR has the additional advantage of being an early clinical trial end point, generally reached within just 2–3 months of treatment initiation [5].

The duration, human resources required for and cost of clinical trials could be reduced if a surrogate end point was to be properly used in place of survival. To date, however, (i) the extent to which the OR is predictive of mortality in the first-line treatment of patients with ED-SCLC has not been fully assessed, even though an association itself between OR and OS has been reported [5]. In addition, (ii) how much time of OS increases as ORR increases in this disease has not been formally

*Correspondence to: Dr K. Hotta, Department of Respiratory Medicine, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama 700-8558, Japan. Tel: +81-86-235-7227; Fax: +81-86-232-8226; E-mail: khotta@md.okayama-u.ac.jp

evaluated. Furthermore, (iii) knowing what factors can affect the association between the ORR and OS would be of interest to generate relevant hypotheses in future studies. Here, we investigated the association between ORR and OS to address each of the above-mentioned points.

methods

search for trials

We searched for trials that had been conducted from January 1990 to August 2008, as previous reports relied on studies that had been conducted within the past 15–20 years. To avoid publication bias, published and unpublished trials were identified through a computer-based search of the PubMed database and abstracts from past conferences of the American Society of Clinical Oncology (1998–2008) using the terms lung neoplasm, carcinoma, small cell, chemotherapy and randomised controlled trial. The search was also guided by a thorough examination of reference lists from original articles, review articles, relevant books and the Physician Data Query registry of clinical trials.

selection of trials

Phase III randomised controlled trials were considered if they compared first-line, systemic chemotherapy for ED-SCLC that included cytotoxic agents, providing year of trial initiation. Trials were excluded if they investigated immunotherapeutic regimens or if they enrolled only responders to the initial round of chemotherapy. Trials that were initially designed to assess combined modality treatments, including radiotherapy and surgery concurrently with the initial chemotherapy, were also considered ineligible, whereas those involving the sequential use of these therapies or prophylactic cranial irradiation (PCI) after the induction of chemotherapy were allowed. Some phase III trials included patients with both LD- and ED-SCLC. These were considered eligible only if survival data for the patients with ED-SCLC could be obtained. The definitions of LD- and ED-SCLC varied somewhat in the different groups, but we could not reallocate the patients because of our inability to access each patient database. Instead, we applied the definitions described in each original report to this study. If no relevant descriptions were documented, we assumed that the definitions in the trial were based on the guidelines that existed at the time the trial was initiated [6, 7]. The control arms in each phase III trial were identified based on the statement in each trial.

data abstraction

To avoid bias in the data-abstraction process, four medical oncologists (IO, NO, YF and KH), one of whom holds a board certificate for medical oncology (KH), independently abstracted the data from the trials and subsequently compared the results. The following information was obtained from each report: the year of trial initiation (year when the first patient was accrued), the number of patients enrolled and randomised, the median patient age, the proportion of patients who had a good performance status (PS), the proportion of patients who were male and who had brain metastasis, the chemotherapeutic regimen, the definition of ED, the description of the administration of sequential thoracic irradiation, surgery or PCI as part of the trial design and the MST (per treatment arm). All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators. For trials with more than two treatment arms, we constructed multiple pairs for the investigational and reference arms.

quantitative data synthesis

To investigate the association between differences in ORR and MST, we defined the MST difference as the difference in MST between the investigation and reference arms; similarly, the ORR difference was defined as the ratio of the ORR in the investigation arm to the ORR in the reference arm (all measures in months). The information from the phase III trials was evaluated using a multiple stepwise regression model (with the following stepping method criteria: probability of F to enter of ≤ 0.05 and to remove of ≥ 0.10) to determine whether the following factors independently affected the MST difference: ORR difference, year of study, definition of ED, ratio of patients with a good PS in the investigational arm to those in the reference arm and a trial design including PCI for those with an OR (CR/PR) to the induction of chemotherapy. All analyses were weighted by trial size. The data were used to determine whether each factor had an independent impact on the survival of patients with ED-SCLC who were treated in the phase III studies. All P values corresponded to two-sided tests; significance was set at $P < 0.05$. The strength of each association was defined a priori using commonly accepted criteria for the proportion of variation (R^2) as follows: 0–0.29, little or no association; 0.30–0.69, moderate or weak association and 0.70–1.00, strong association [8].

results

trials included in the analysis

Of the 2166 trials screened, 48 trials for ED-SCLC were identified as having data regarding OS and ORR (Figure 1). A total of 8779 patients were randomly allocated to 100 chemotherapeutic arms. Of these 48 trials, two had three treatment arms and one had four treatment arms; thus, 52 trial pairs were in the investigational arm versus the reference arm (Table 1). Of these trials, most had high proportions of male patients and patients with a good PS. The response criteria were described in 43 of the 52 trials. Approximately half of the trials used the response criteria of the World Health Organisation (WHO). Regarding the chemotherapeutic regimens, cisplatin plus etoposide-containing regimens were most frequently evaluated in both the investigational and reference arms (25 and 27 arms, respectively), while a cyclophosphamide, adriamycin and vincristine regimen was used in 17 and 23 arms, respectively.

degree of association between the MST and ORR differences

We plotted the MST and ORR differences (Figure 2). A modest relationship was detected between the ORR and MST differences ($R^2 = 0.3314$), suggesting that the ORR difference between the investigational and reference arms could predict 33.1% of the variance in the MST difference between the arms.

Next, we assumed that this association would be closer if the trials were limited to those in which the response criteria were clearly defined; the relationship between the two parameters, however, was not as so different as expected ($n = 43$; $R^2 = 0.1949$). In addition, we assessed whether the association could be affected by the type of response criteria, but it was nearly consistent irrespective of using the WHO criteria for response assessment [$R^2 = 0.1340$ ($n = 23$) versus 0.2765 ($n = 20$) for those trials in which the WHO criteria and other criteria were used, respectively].

To rule out potential confounding variables between the ORR difference and other trial characteristics, we conducted a multiple linear regression analysis for the MST difference. The stepwise multiple regression model used excluded all covariates

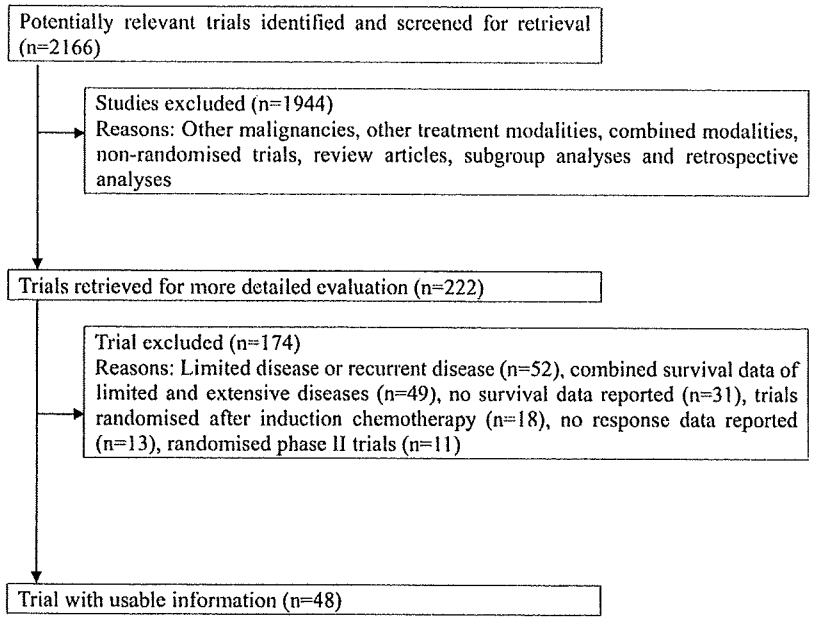

Figure 1. Flowchart showing the review process for the trials.

Table 1. Trial demographics and chemotherapeutic regimens in the 52 trial pairs

Trial characteristics	
Median no. of randomly assigned patients per trial (range)	142 (33–784)
Published year (median, range)	1997 (1990–2008)
Year of trial initiation (median, range)	1990 (1983–2006)
Percentage of patients with a good PS (median, range)	80 (35–100)
Percentage of male patients (median, range)	81 (56–93)
Trials including the administration of PCI to those with an objective response to the initial treatment (yes/no)	20/32
Definition of extensive disease (yes/no)	36/16
Description of the response criteria (yes/no)	43/9
World Health Organisation	23
European Cooperative Oncology Group	2
RECIST	1
Japan Lung Cancer Society	1
Described, but no criteria type documented	16

Good PS was defined as a PS of zero or one.
PS, performance status; PCI, prophylactic cranial irradiation; RECIST, response evaluation criteria in solid tumours.

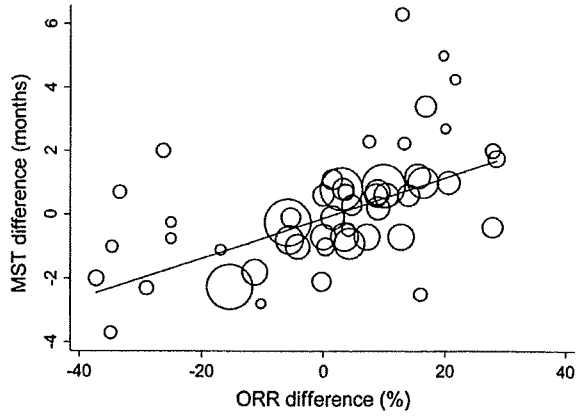

Figure 2. Correlations between the median survival time (MST) difference between the investigational and reference arms and differences in the objective response rate (ORR) in the eligible trial pairs weighted by the number of randomised patients ($R^2 = 0.3314$). The R^2 scores suggest that the ORR difference between the investigational and reference arms could explain 33.1% of the variance in the MST difference between the arms. Each trial is represented by a circle; the size of each circle is proportional to the number of randomised patients.

except the ORR difference. This turned out to be a significant factor affecting the MST difference ($P = 0.003$); however, only 31.6% of the variance in the MST ratio was accounted for even by this model ($R^2 = 0.3156$).

association between the MST and ORR differences in several subgroups

To investigate whether the trial setting could affect the relationship between the MST and ORR differences, eligible

Table 2. Degree of association between the ORR and MST differences in various clinical settings in the simple regression analysis

	No. of trials	Regression coefficient	R^2
Overall	52	0.063	0.3314
Various subgroups			
Trials including PCI for those with an objective response to the initial therapy			
Yes	20	0.083	0.6279
No	32	0.053	0.2254
CAV regimen			
Yes	24	0.062	0.3302
No	28	0.063	0.3264
PE regimen			
Yes	32	0.062	0.3376
No	20	0.064	0.3185
Trial design of additional thoracic irradiation			
Yes	14	0.061	0.4954
No	38	0.063	0.2937
Published year			
1996 or before	26	0.037	0.2346
1997 or later	26	0.094	0.4671
% of good PS patients			
≥80[a]	12	0.061	0.3351
<80[a]	13	0.092	0.4505

All analyses were weighted by trial size.
[a]Median percent of patients with good PS.
ORR, objective response rate; MST, median survival time; R^2, the proportion of variation; PCI, prophylactic cranial irradiation; CAV, cyclophosphamide, doxorubicin and vincristine; PE, cisplatin and etoposide; PS, performance status.

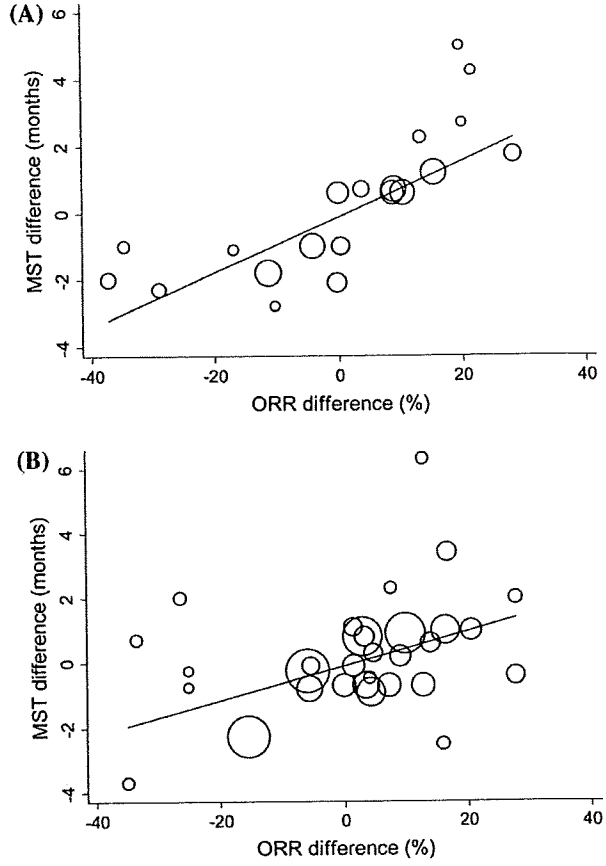

Figure 3. Correlations between the median survival time (MST) difference and objective response rate (ORR) difference between the investigational and reference arms in trials (**A**) designed to administer prophylactic cranial irradiation (PCI) to those with an objective response to the inductive therapy (R^2 = 0.6279) or (**B**) not (R^2 = 0.2254). The analysis was weighted by the number of randomised patients. The R^2 scores suggest that the ORR difference between the investigational and reference arms could explain as much as 62.8% of the variance in the MST difference between the arms in trials including PCI, while in the trials without PCI, the MST difference was less exactly accounted for by the ORR difference (22.5%). Each trial is represented by a circle; the size of each circle is proportional to the number of randomised patients.

trial pairs were divided into several subgroups (Table 2). We found a stronger association between the two parameters for those trials in which all the patients with an OR to the initial chemotherapy were given PCI (R^2 = 0.6279; Figure 3A), whereas a weaker association was found in those trials without that type of design (R^2 = 0.2254; Figure 3B). None of the other characteristics assessed seemed to affect the association (Table 2).

predicted MST difference based on the fitted model for those trials with the PCI setting

We next constructed a fitted formula for predicting the MST difference using the actual ORR difference for those trials that included PCI as part of their design in which a high R^2 value was obtained:

Predicted MST difference between the investigational and reference arms = 0.083 × (actual ORR difference) − 0.125.

The predicted MST differences are listed in Table 3 according to the various ORR differences. For example, when the investigational regimen was expected to yield a 10% increase in the ORR as compared with the state-of-the-art regimen, the MST was predicted to increase only by 0.7 months (21.2 days) in the investigational arm.

discussion

In this study, we found a modest association between the ORR and MST differences in the complete trial (R^2 = 0.3314; Figure 2). In contrast, the design of PCI setting for all responders to the initial chemotherapy favourably affected the relationship (R^2 = 0.6279; Figure 3A). In this setting, large differences in ORR were needed to predict a survival benefit (1.2-day survival advantage per 2% increase in ORR).

Note that the relationship was stronger only for those trials in which PCI was assigned to all patients with an OR to the initial treatment (R^2 = 0.6279; Figure 3A). One would postulate that this result is related to the ability of anticancer agents to penetrate the blood–brain barrier (BBB). Apart from clinically

Table 3. Predicted MST difference according to the ORR difference

ORR difference[a] (%)	Predicted MST difference[a], months (days)
2.5	0.1 (2.5)
5.0	0.3 (8.7)
7.5	0.5 (14.9)
10.0	0.7 (21.2)
12.5	0.9 (27.4)
15.0	1.2 (33.6)
17.5	1.4 (39.8)
20.0	1.6 (46.1)

[a]Difference between the investigational and reference arms. For example, when an investigational regimen was expected to yield a 10% increase in the ORR as compared with the standard regimen, the MST was predicted to increase by 0.7 months (21.2 days) in the investigational arm.
ORR, objective response rate; MST, median survival time.

obvious cranial metastases, which would be sensitive to systemic chemotherapy because of an impaired BBB [9], radiologically undetected micrometastases in the brain, which are common in patients with ED-SCLC, are generally considered to be insensitive to chemotherapy because they are able to hide behind the still-intact BBB [9]. Thus, even if systemic chemotherapy was effective against detectable extracranial diseases, such small undetectable cranial diseases could continue to grow without the use of PCI, possibly resulting in a poor outcome. That could explain why a tight association was not observed between the radiological response and survival data. However, with the PCI setting for responders to the initial chemotherapy, such a difference in the response pattern between extracranial and intracranial diseases would theoretically be minimised. This may be why a stronger association between the radiological response and survival was observed when only those trials that included PCI as part of their design were assessed in the analysis (Figure 3A). This hypothesis requires further study. Other clinical factors including PS examined did not seem to influence the relationship between ORR and MST (Table 2), while a number of studies have shown that PS has impacts on outcome [10–12]. This would simply reflect that good PS patients can respond well to chemotherapies and survive longer and that poor PS patients hardly respond to them, resulting in the poor outcome.

In addition, knowing how much of a difference in ORR is needed to predict an obvious survival difference in ED-SCLC is also clinically necessary. In their abstracted database study, Johnson et al. [13] investigated the role of ORR as a surrogate marker in the treatment of advanced non-small-cell lung cancer (NSCLC) by comparing incremental differences in MST between the arms with those in ORR. The formula they used to predict the MST difference was nearly identical to ours, except for the difference in cancer type: MST difference = 0.090 × (the ORR difference) − 0.048. Using this formula for patients with NSCLC, if the investigational regimen was expected to yield a 10% increase in the ORR as compared with the standard regimen, the MST was predicted to increase by only 0.9 months (25.6 days) in the investigational arm. Given either formula, one could intuitively predict the survival benefit of a new therapy by comparing the OR data from their early clinical trials with the ORR for the state-of-the-art therapy. At any rate, both sets of results indicate that, irrespective of the small- or non-small-cell subtype, the survival advantage would be small even if a relatively large ORR difference was obtained.

Few randomised trials of metastatic lung cancer have reported hazard ratios, and predictions based on this measure would not be representative and could be biased. Additionally, differences in follow-up duration between trials could affect the calculated hazard ratios. For these reasons, the MST was used in this study to ensure that all trials were long enough to capture the relevant end points in at least half of the patients. The reason for this pragmatic approach is that the value of a treatment of metastatic disease is usually measured in terms of incremental survival gains rather than the proportional or absolute risk of death [13].

Trial-level surrogacy as described here is not necessarily linked to individual-level surrogacy; thus, our data cannot be used to predict an individual's chance of survival on the basis of their response to treatment. Analyses based on data derived from both sources have strengths and weaknesses [14]. Although the use of individual patient data (IPD) restricts the analysis to a limited number of trials and the analysis is not easily replicated by independent researchers, it allows better characterisation of important covariates that affect survival. Future investigations using IPD could show a more precise relationship between survival and the response to treatment. In addition, as a point to be discussed, assessment of response rate would be variable and unreliable. It is well documented that response rates have dropped in recent years as more rigorous criteria are used. This is borne out by the fact that the correlation dropped in studies with clearly defined response criteria. Using differences in response rates rather than absolute values would help address this.

In conclusion, in this study, we found a favourable relationship between the ORR and MST differences for trials in which those who responded to the initial chemotherapy subsequently received PCI. Given the recent finding of a survival advantage from PCI even in patients with ED-SCLC [15], the frequency at which PCI is used for responders to the initial treatment will likely increase. Considering such circumstances, ORR data may be useful for predicting how much improvement in OS can be obtained. In contrast, large differences in ORR are needed to predict a survival benefit, strongly suggesting the need for the development of new chemotherapeutic agents in ED-SCLC.

funding

There is no funding source in this study.

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CORRESPONDENCE

Prophylactic Cranial Irradiation in Small-Cell Lung Cancer

TO THE EDITOR: The trial reported by Slotman et al. (Aug. 16 issue)[1] showed a reduced incidence of symptomatic brain metastases and an improvement in overall survival with the addition of prophylactic cranial irradiation in patients with extensive-stage small-cell lung cancer. Brain imaging was not part of standard staging before randomization unless symptoms suggestive of metastasis were present. Published data suggest that up to 15% of patients have asymptomatic brain metastases, and the prognosis for these patients is similar to that for patients with symptomatic metastases.[2,3] Therefore, the benefit of prophylactic cranial irradiation may be less than that suggested because some patients probably had brain metastases at diagnosis.

The authors note that the high extracranial-progression rate should be given priority for future investigations. The role of thoracic radiation therapy in limited-stage small-cell lung cancer is well established.[4] Although systemic therapy is the primary treatment of extensive-stage disease, thoracic irradiation may provide an additional benefit. Jeremic et al. found that there was a 5.4% improvement in overall survival when thoracic irradiation was given after chemotherapy.[5] This type of aggressive local approach should be considered for future trials.

Anand T. Shivnani, M.D.
Baylor–Irving Cancer Center
Irving, TX 75061
anand.shivnani@usoncology.com

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TO THE EDITOR: Two pieces of essential information were not reported by Slotman et al. First, there are no data in their report regarding the use of standard chemotherapeutic regimens as induction therapy and whether these regimens, if used, were well balanced between the study groups. Second, the authors did not describe the tumor response to induction chemotherapy. Patients with a complete response are most likely to benefit from prophylactic cranial irradiation,[1,2] but the patients enrolled in this study were not stratified according to the response category at the time of randomization. We would also like to know whether patients with a partial response to the induction therapy, as well as those with a complete response, could benefit substantially from the use of prophylactic cranial irradiation.

Yoshiro Fujiwara, M.D.
Katsuyuki Hotta, M.D., Ph.D.
Katsuyuki Kiura, M.D., Ph.D.
Okayama University
Okayama 700-8558, Japan

THIS WEEK'S LETTERS

1. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. N Engl J Med 1999;341:476-84.
2. Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer 2001;1:5.

TO THE EDITOR: Slotman and colleagues have contributed an important study. One weakness in the design was the heterogeneity introduced by allowing several radiotherapy regimens with a wide range of biologically equivalent doses — 25 to 39 Gy by the authors' calculations. Although assessment for a dose–response relationship was not part of the study design, did the authors detect such a relationship among these regimens? Also, would the authors comment on whether their findings would affect their management of extrapulmonary neuroendocrine primary cancers?

Shiv R. Khandelwal, M.D.

University of Virginia
Charlottesville, VA 22908

Maya Ghaemmaghami, M.D.

Augusta Medical Center
Fishersville, VA 22939

THE AUTHORS REPLY: In our study, brain imaging was not mandatory for patients with extensive-stage small-cell lung cancer who did not have related symptoms, an approach that is in accordance with the prevailing guidelines.[1] Only 29% of randomized patients underwent brain imaging at diagnosis, and Dr. Shivnani suggests that this was a drawback in our study because some patients may have had asymptomatic brain metastases at randomization. However, the magnitude of the survival benefit with prophylactic cranial irradiation is such that it cannot be explained by an effect on existing metastases.[2] We concur that further evaluation of the role of chest radiotherapy is warranted, and such a trial is now in preparation.

Fujiwara et al. question the absence of detailed data on chemotherapy regimens used and also on potential imbalances of chemotherapy between the study groups. Most patients were treated with four to six cycles of cisplatin–etoposide, carboplatin–etoposide, cyclophosphamide–doxorubicin–etoposide, or carboplatin–paclitaxel. To reduce the risk of bias, randomization included stratification according to institution but not according to chemotherapy. Patients who had any response were eligible, since response evaluation in patients with extensive disease can be difficult (e.g., for bone metastases), and it is not standard practice. As we reported, 76% of patients had evidence of residual tumor at the primary site, and 71% had evidence of tumor at distant sites. Since a total of 87% of study patients had some residual disease, our study clearly shows the benefit of cranial irradiation after a partial response. A previous meta-analysis included patients with extensive disease who had had a complete response,[3] and the current data support the use of prophylactic cranial irradiation in all patients with small-cell lung cancer who have a response to chemotherapy.

In response to Drs. Khandelwal and Ghaemmaghami, we can confirm that no significant differences were observed in patient characteristics, the incidence of brain metastases, survival, or side effects between patients receiving 20 Gy in five fractions (62% of all patients) and those receiving treatment with the more fractionated schemes. Extrapulmonary small-cell cancer is most likely to benefit in the same way that small-cell lung cancer does. However, the role of prophylactic cranial irradiation for extrapulmonary neuroendocrine tumors or other neuroendocrine tumors of the lung is an unanswered question that needs to be investigated in new trials.

Ben Slotman, M.D., Ph.D.
Pieter Postmus, M.D., Ph.D.
Suresh Senan, Ph.D.

VU University Medical Center
1081 HV Amsterdam, the Netherlands
bj.slotman@vumc.nl

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