Depression Rating by Patients

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate the level of depression (Zigmond & Snaith, 1983). This questionnaire consists of a seven-item anxiety subscale and a seven-item depression subscale. It assesses the patients' mental status over the preceding week. We have previously established the reliability and validity of the Japanese version of this questionnaire in cancer patients (Kugaya et al., 1998). The optimal cutoff point for screening of patients with adjustment disorder or major depressive disorder and with major depressive disorder was >10 and >20, respectively (Kugaya et al., 1998).

Sociodemographic and Medical Factors

An *ad hoc* self-administered questionnaire was used to obtain information on the sociodemographic status, including marital status, level of education, and employment status. Performance status as defined by the Eastern Cooperative Oncology Group (ECOG) was evaluated by the attending physicians. All other medical information (clinical stage and anti-cancer treatment) was obtained from the patients' charts.

Depression Rating by the Attending Physicians

An attending physician rated the severity of depression in each patient using a 3-point Likert scale (0 [*absent*], 1 [*present but not interfering with daily life (care not needed)*], 2 [*present and interfering with daily life (care needed)*]) during or just after the patients' visit to the outpatient clinic.

Definition of Underrecognition of Depression

Depression was considered to be underrecognized when the patients had a HADS score above the cutoff value for screening of patients with adjustment disorder or major depressive disorder but in whom the depression rating by the attending physician was 0.

Statistical Analysis

The presence or absence of underrecognition was entered into the analyses as the dependent variable. Univariate analyses were carried out to determine the potential correlated factors. Intergroup comparisons of categorical and continuous variables were conducted using the chi-squared test, Fisher's exact test, and the unpaired t test, respectively.

RESULTS

Patient Characteristics

Data were available for 60 cancer patients (Table 1). The mean age was 65.1 years (*SD*, 10, range, 43–83) and the mean number of days after the diagnosis was 263 (*SD*, 380, range, 24–2,226). Of all the patients, 78% were male, and 82% had advanced cancer (Stage IIIb or IV or recurrence).

Prevalence of Underrecognition of Depression

Depression was underrecognized by the physicians in 44 (73%) patients (Table 2). There were no significant difference in rate of depression underrecognition by physicians between patients with adjustment disorder level distress and those with major depression level distress ($\chi^2 = 0.09$, $df = 1$, $p = .76$).

Factors Correlated with Underrecognition of Depression by the Physicians

Univariate analyses revealed that none of the factors related to the reluctance for emotional disclosure was associated with the underrecognition of depression by the physicians (Table 3). None of the demographic and cancer–related variables were associated with the underrecognition of depression.

Table 1. *Demographical and Clinical Characteristics of Patients (N = 60)*

Sample characteristic	*N*	%	
Age (year)			mean: 65.1 ± 10 (range, 43–83), median: 65.5
Sex			
Male	47	78	
Clinical stage			
I-IIIA	11	18	
IIIB	22	37	
IV	26	43	
Recurrent	1	2	
Days after diagnosis			mean: 263 ± 380 (range, 24–2226), median: 140
Performance status			
0	47	78	
1	9	15	
2	4	7	
Anti-cancer treatment within a month			
Surgery	0	0	
Chemotherapy	43	72	
Radiation therapy	7	12	

Table 2. *Comparison of Depression Ratings by the Attending Physicians and by the Patients*

Depression rating by the attending physicians	Depression rating by the patients[a]: Adjustment disorder level (11–19)	Major depression level (≥20)	Total
Absent	*32 (74%)*	*12 (71%)*	*44 (73%)*
Present but not interfering with daily life (care not needed)	11 (26%)	4 (24%)	15 (25%)
Present and interfering with daily life (care needed)	0 (0%)	1 (6%)	1 (2%)
Total	43 (100%)	17 (100%)	60 (100%)

Italics indicate underrecognition of depression by the physicians.
[a]Hospital Anxiety and Depression Scale total score.

DISCUSSION

The present findings did not support the hypothesis that the reluctance of cancer patients to share their psychological distress with the treating physicians was associated with the underrecognition of depression by the treating physicians.

To the best of our knowledge, this is the first study that examined patients' reluctance for emotional disclosure as a barrier to the recognition of the psychological distress in the patients by the treating physicians in the cancer setting. One of the few studies that focused on this issue in the primary care setting was from New Zealand (Bushnell et al., 2005). They reported that the level of identification of psychological symptoms and psychiatric diagnosis by general practitioners was not associated with the patients' reported unwillingness for emotional disclosure. Although their study was different from ours in many respects, including the patient characteristics, method of assessment of depression and reluctance for emotional disclosure, and the definition of underestimation, taken together, these results may indicate that the reluctance for emotional disclosure may not play a very significant role in the underestimation of depression. One possibility is that other patient factors, for example, nonverbal emotional expression, might influence the physicians' recognition of the patients' psychological status. Presence of families or relatives along with patients during the clinical consultation might be one of other confounding factors, because family members are important proxy to report patients' condition to physicians in Japan. Another important possibility is that the sample size might be too small to find the impact of the reluctance for emotional disclosure on depression recognition by physicians. That could not be avoided because of the nature of the secondary analysis. Also other factors such as provider

Table 3. *Factors Correlated with Underrecognition of Depression by the Physicians*

Sample characteristics		Underrecognition ($N = 44$)		No underrecognition ($N = 16$)		
		N	(%)	*N*	(%)	*p* value
Sex	Male	34	77	13	81	0.74[a]
Education	Junior high school or less	15	34	4	25	0.75[b]
Marital status	Married	32	73	13	81	0.74[b]
Job	Working outside the home	12	27	3	19	0.74[b]
ECOG Performance Status	1 or worse	37	84	14	88	1.00[b]
Living status	Alone	8	18	3	19	1.00[b]
Disease stage	IIIb, IV, or recurrence	37	84	12	75	0.46[b]
Confidants	Presence	42	95	13	81	0.11[b]
		Mean	*SD*	Mean	*SD*	*p*
Age		65.4	10.1	64.3	10.1	0.73[c]
Reluctance for emotional disclosure	No perceived need	2.1	0.9	2.4	0.8	0.23[c]
	Fear of negative impact	1.5	0.8	1.6	0.9	0.91[c]
	Negative attitude	1.9	0.9	1.8	0.6	0.42[c]
	Hesitation to disturb physicians	2.7	1.0	2.5	0.9	0.51[c]

[a]Chi-square test. [b]Fisher's exact test. [c]Unpaired *t* test.

factors, system and environmental factors, and interactions between these factors might be play a role in depression recognition. These should be taken into account in future studies.

We acknowledge that the results must be interpreted with caution for several reasons. First, although the questionnaire used to investigate the reluctance for emotional disclosure has been validated, there remains the possibility that the attitudes assessed using the questionnaire in this study might not be concordant with the actual behavior of the patients. Second, depression was not assessed by psychiatric interviews, such as the Structured Clinical Interview for DSM-IV-TR, which is thought to be a gold standard to diagnose depression in patients. Also the definition of underrecognition of depression in the patients was *post hoc*. Third, only two physicians were included in this study. Fourth, this was conducted in a university hospital and included Japanese outpatients with lung cancer. These facts may limit the generalizability.

This study indicated, consistent with the many previous reports, a high prevalence and frequent underrecognition of depression among cancer patients. Because of these limitations, we should still be cautious in assuming that the reluctance of patients for emotional disclosure may not contribute significantly to underrecognition of depression in clinical practice. To resolve this critical problem, further investigation into this phenomenon and its associated factors and barriers is warranted.

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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

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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

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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

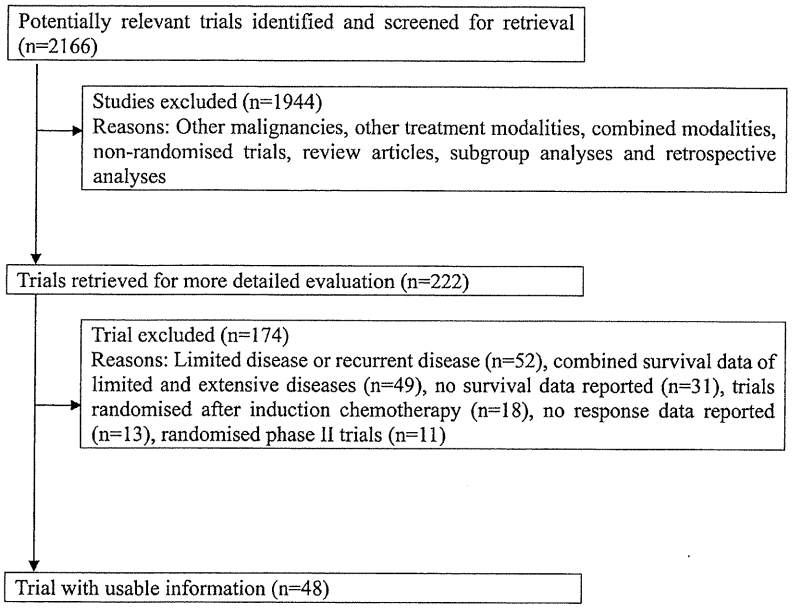

Figure 1. Flowchart showing the review process for the trials.

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.

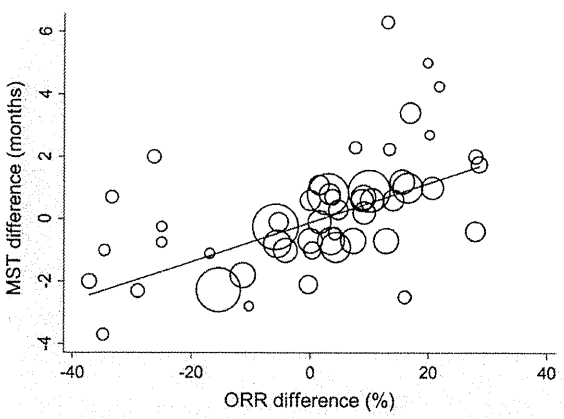

Figure 2. Correlations between the median survival time (MST) difference between the investigational and reference arms and differences in the objective response rate (ORR) in the eligible trial pairs weighted by the number of randomised patients ($R^2 = 0.3314$). The R^2 scores suggest that the ORR 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.

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.

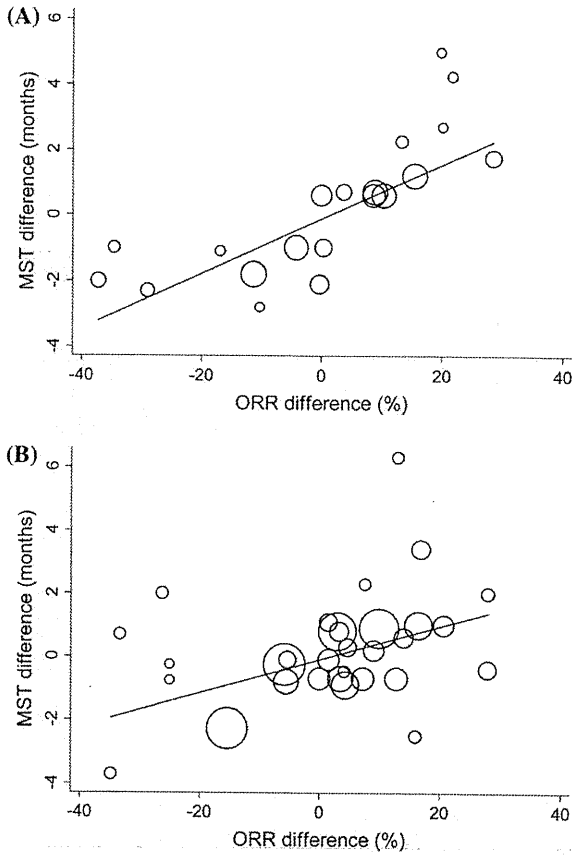

Figure 3. Correlations between the median survival time (MST) difference and objective response rate (ORR) difference between the investigational and reference arms in trials (**A**) designed to administer prophylactic cranial irradiation (PCI) to those with an objective response to the inductive therapy (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.

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.

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