Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial

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Summary

Background Results from a previous phase 3 study suggested that prophylactic cranial irradiation reduces the incidence of symptomatic brain metastases and prolongs overall survival compared with no prophylactic cranial irradiation in patients with extensive-disease small-cell lung cancer. However, because of the absence of brain imaging before enrolment and variations in chemotherapeutic regimens and irradiation doses, concerns have been raised about these findings. We did a phase 3 trial to reassess the efficacy of prophylactic cranial irradiation in the treatment of extensive-disease small-cell lung cancer.

Methods We did this randomised, open-label, phase 3 study at 47 institutions in Japan. Patients with extensive-disease small-cell lung cancer who had any response to platinum-based doublet chemotherapy and no brain metastases on MRI were randomly assigned (1:1) to receive prophylactic cranial irradiation (25 Gy in ten daily fractions of 2·5 Gy) or observation. All patients were required to have brain MRI at 3-month intervals up to 12 months and at 18 and 24 months after enrolment. Randomisation was done by computer-generated allocation sequence, with age as a stratification factor and minimisation by institution, Eastern Cooperative Oncology Group performance status, and response to initial chemotherapy. The primary endpoint was overall survival, analysed in the intention-to-treat population. This trial is registered with the UMIN Clinical Trials Registry, number UMIN000001755, and is closed to new participants.

Findings Between April 3, 2009, and July 17, 2013, 224 patients were enrolled and randomly assigned (113 to prophylactic cranial irradiation and 111 to observation). In the planned interim analysis on June 18, 2013, of the first 163 enrolled patients, Bayesian predictive probability of prophylactic cranial irradiation being superior to observation was 0·011%, resulting in early termination of the study because of futility. In the final analysis, median overall survival was 11·6 months (95% CI 9·5–13·3) in the prophylactic cranial irradiation group and 13·7 months (10·2–16·4) in the observation group (hazard ratio 1·27, 95% CI 0·96–1·68; p=0·094). The most frequent grade 3 or worse adverse events at 3 months were anorexia (six [6%] of 106 in the prophylactic cranial irradiation group *vs* two [2%] of 111 in the observation group), malaise (three [3%] *vs* one [<1%]), and muscle weakness in a lower limb (one [<1%] *vs* six [5%]). No treatment-related deaths occurred in either group.

Interpretation In this Japanese trial, prophylactic cranial irradiation did not result in longer overall survival compared with observation in patients with extensive-disease small-cell lung cancer. Prophylactic cranial irradiation is therefore not essential for patients with extensive-disease small-cell lung cancer with any response to initial chemotherapy and a confirmed absence of brain metastases when patients receive periodic MRI examination during follow-up.

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Introduction

Meta-analyses[1,2] have shown a decrease in incidence of brain metastases and an improvement in survival of patients with small-cell lung cancer who receive prophylactic cranial irradiation versus observation after achieving complete responses to initial chemotherapy or chemoradiotherapy. In 2007, the European Organisation for Research and Treatment of Cancer (EORTC) published the results of a study in which 286 patients with extensive-disease small-cell lung cancer who had had any response to initial chemotherapy were randomly assigned to receive prophylactic cranial irradiation or observation.[3] The investigators reported that the cumulative risk of symptomatic brain metastases within 1 year was 14·6% in the prophylactic cranial irradiation group and 40·4% in the control group; 1-year survival was 27·1% and 13·3%, respectively. Thus, the investigators concluded that prophylactic cranial irradiation reduces the incidence of symptomatic brain metastases and increases overall survival when compared with observation.

However, several concerns have been raised about the EORTC study. First, although a previous study had reported that asymptomatic brain metastases are present in about 15% of patients with small-cell lung cancer at diagnosis,[4] in the EORTC study brain imaging was not a standard

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Research in context

Evidence before this study

We searched PubMed with the terms "small cell lung cancer", "extensive", and ""prophylactic cranial irradiation" for reports of randomised clinical trials published in any language up to Nov 30, 2016. We also searched the reference lists of articles identified by this search. Meta-analyses have shown a decrease in the incidence of brain metastases and an improvement in the survival of patients with small-cell lung cancer who receive prophylactic cranial irradiation after achieving complete responses to initial chemotherapy or chemoradiotherapy. Investigators of one randomised trial (European Organisation for Research and Treatment of Cancer [EORTC]) reported that prophylactic cranial irradiation reduced the incidence of symptomatic brain metastases and resulted in longer overall survival compared with observation in patients with extensive-disease small-cell lung cancer who had had any response to initial chemotherapy. However, absence of brain imaging before enrolment and substantial variations in radiation doses and fractions might have influenced the results.

Added value of this study

Our findings suggest that prophylactic cranial irradiation reduces the incidence of brain metastases, but does not increase progression-free survival or overall survival compared with observation alone in patients with extensive-disease small-cell lung cancer with a confirmed absence of brain metastases by MRI.

Implications of all the available evidence

On the basis of the results of this Japanese trial, we conclude that prophylactic cranial irradiation is not essential for patients with extensive-disease small-cell lung cancer with any response to initial chemotherapy and a confirmed absence of brain metastases by MRI when patients receive periodic MRI examination during follow-up and treatment of asymptomatic metastases.

component of initial staging or follow-up unless symptoms suggestive of brain metastases were present. The EORTC study might therefore have included a substantial number of patients who already had brain metastases at randomisation. Second, although cisplatin-containing regimens are associated with a higher proportion of patients achieving a response and a higher probability of survival than are regimens without cisplatin in patients with small-cell lung cancer,[5] the EORTC study did not report the proportion of patients treated with cisplatin-containing regimens. Furthermore, although patients who achieve complete response are known to be most likely to benefit from prophylactic cranial irradiation,[1,2] the investigators did not document the proportion of patients who achieved complete response. Third, substantial variations in the total irradiation dose (20–30 Gy) and the number of fractions administered (five to 12) resulted in patients receiving a wide range of biologically equivalent doses (28–39 Gy; calculated with an α/β ratio of 10 Gy). Finally, although prophylactic cranial irradiation has been regarded as a standard treatment for patients with small-cell lung cancer who achieve a complete response because it was shown to increase survival, the EORTC study was designed to assess whether this treatment reduces the incidence of symptomatic brain metastases. In view of these concerns, we did a phase 3 trial to reassess the efficacy of prophylactic cranial irradiation in the treatment of extensive-disease small-cell lung cancer.

Methods

Study design and participants

We did this randomised, open-label, phase 3 study at 47 institutions in Japan (appendix pp 1–2). Patients were eligible for enrolment if they met the following criteria: cytologically or histologically confirmed extensive-disease small-cell lung cancer (defined as disease beyond one hemithorax including ipsilateral hilar, bilateral mediastinal, and bilateral supraclavicular lymph node metastases, and malignant pleural or pericardial effusion) before the start of initial chemotherapy; age 20 years or older; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; any response assessed after completion of two or more cycles of initial platinum-based doublet chemotherapy (either cisplatin or carboplatin combined with one non-platinum agent); absence of brain metastases confirmed by gadolinium-enhanced MRI (non-gadolinium-enhanced MRI scans were acceptable if contraindicated) within 4 weeks before enrolment; absence of tumour regrowth confirmed by thoracoabdominal CT (either contrast-enhanced or plain scan acceptable) within 4 weeks before enrolment; an interval of no more than 6 weeks between the start of the last initial chemotherapy and enrolment; and an estimated life expectancy of 3 months or more. Responses to initial platinum-based doublet chemotherapy were categorised as complete response, partial response, and minor response. Complete response and partial response were defined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. In patients with measurable lesions, minor response was defined as between a 5% and 30% decrease in the sum of diameters of target lesions in accordance with RECIST 1.1, whereas in patients without measurable lesions before initial chemotherapy, minor response was defined as disappearance or shrinkage of some, but not all, lesions with no unequivocal progression. Responses were assessed by the local investigators and confirmation of response was not required.

See Online for appendix

Exclusion criteria were a history of radiotherapy to the irradiation field for prophylactic cranial irradiation, any active concomitant malignancy, any mental disorder or

somatic comorbidities of clinical concern, pregnancy or lactation, and women with childbearing potential. All patients provided written informed consent before being enrolled in the study. The study protocols were approved by the institutional review boards of the participating institutions. The protocol is available in the appendix.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive prophylactic cranial irradiation or observation. Staff at the West Japan Oncology Group Data Center (Osaka, Japan) used a computer-generated allocation sequence and assigned patients to groups. Investigators did not have access to the allocation sequence: randomisation was done via a computer program developed by an outside contract research organisation (EPS, Tokyo, Japan), with a follow-up fax to notify investigators at each site of the allocation result. The random assignment incorporated age (<70 years *vs* ≥70 years) as a stratification factor. In each stratum, dynamic allocation was done by the minimisation method with the following three adjustment factors: institution, ECOG performance status (0–1 *vs* 2), and response to initial chemotherapy (complete response *vs* partial or minor response). Patients and investigators were not masked to treatment allocation.

Procedures

All patients had brain MRI and thoracoabdominal CT within the 4 weeks before enrolment. Patients allocated to the prophylactic cranial irradiation group underwent cranial radiation at a total dose of 25 Gy delivered in ten daily fractions (2·5 Gy per fraction) using parallel opposing fields with a 4–10 MV linear accelerator with source-axis distance of at least 100 cm. Prophylactic cranial irradiation had to be started within 3–8 weeks after start of the previous cycle of chemotherapy. In both treatment groups, no systemic chemotherapy was allowed until the detection of extracranial or intercranial progression or recurrence by imaging. Determination of brain metastasis was done using RECIST criteria and by MRI. Progression was determined by using RECIST and by the local investigator. Palliative radiotherapy for sites other than the brain for the purpose of symptom alleviation was allowed in both groups.

All patients, irrespective of the presence or absence of neurological symptoms, were required to have brain MRI at 3-month intervals up to 12 months and at 18 and 24 months after enrolment, unless there were compelling reasons not to adhere to this protocol, such as patient refusal and physician judgment. Development of symptoms suggestive of brain metastases required brain MRI, or in some cases brain CT, to confirm or exclude the presence of brain metastases. If extracranial progression was suspected on the basis of symptoms or abnormal laboratory test values, the suspected sites of disease progression were to be examined by imaging tests as early as possible according to each institution's policy.

Toxicities related to prophylactic cranial irradiation, such as alopecia, dermatitis, headache, anorexia, nausea, vomiting, dizziness, malaise, lethargy, and muscle weakness (lower limb), were assessed at randomisation, just after prophylactic cranial irradiation (intervention group only) and at the same time as brain MRI (both groups) in accordance with the National Cancer Institute Common Terminology Criteria (CTC) version 3.0. Laboratory monitoring was done according to each institutional policy. Cognitive function was assessed by mini mental state examination (MMSE) before and 12 and 24 months after randomisation. MMSE is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. Physicians administered the questionnaire in person. We chose the MMSE because of familiarity of physicians in Japan with this questionnaire when assessing cognitive impairment in general practice.

Outcomes

The primary endpoint for comparing prophylactic cranial irradiation with observation was overall survival (calculated from the date of randomisation until the date of death from any cause). Secondary endpoints were time to brain metastasis (calculated from the date of randomisation until the date of diagnosis of brain metastasis on the basis of either brain MRI at protocol-specified intervals or brain MRI or CT performed because of the presence of symptoms suggestive of brain metastasis), progression-free survival (calculated from the date of randomisation until the date of documented progression or death from any cause), adverse events, and MMSE scores.

Statistical analysis

The hazard ratio (HR) for death in the prophylactic cranial irradiation group compared with the observation group was 0·68 (95% CI 0·52–0·88) in the EORTC study,[3] and 0·77 (0·54–1·11) in the subset of patients with extensive-disease small-cell lung cancer in a meta-analysis.[1] On the basis of these results, the HR for death in this study was assumed conservatively to be 0·75. Previous phase 3 trials in patients with extensive-disease small-cell lung cancer in Japan have shown 2-year survival of 19·5% with cisplatin and irinotecan[6] and 11% with carboplatin and etoposide.[7] We therefore assumed 2-year survival in our observation group to be 15%. On the assumption of a 2-year overall survival of 24·1% in the prophylactic cranial irradiation group versus 15% in the observation group (HR 0·75), a sample size of 330 with 6 years of accrual and 2 years of follow-up was designed to provide at least 80% power for detecting a significant difference between groups with a one-sided α of 5%. We adopted one-sided α on the basis of the following consideration: when the prophylactic cranial irradiation group is inferior to the observation group, observation remains the standard treatment whether or not the prophylactic cranial irradiation group is

significantly inferior to the observation group. That is, the statistical significance of inferiority of the prophylactic cranial irradiation group to the observation group would not contribute to clinical decision making. This consideration led to the choice of a one-sided test.

The primary endpoint of overall survival after randomisation was analysed with a log-rank test, stratified by age and ECOG performance status. Assessment of the proportional hazards assumption was done by a graphical approach with log-log plots (appendix p 3). Overall survival was estimated with data from the intention-to-treat population (all randomised patients) by the Kaplan-Meier method and HR was generated with a Cox regression model.

The cumulative incidence of brain metastases was calculated and compared between the two groups in the intention-to-treat population by Gray's test.[8] Cases of extracranial progression were not censored for the analysis of time to brain metastasis, but patients continued to be followed up for brain metastases. Progression-free survival was estimated by the Kaplan-Meier method and analysed with the log-rank test with data from the intention-to-treat population. Median follow-up was calculated by determining the median of the pooled data from censored patients. Adverse events were compared between groups with data from the safety analysis population (all patients who were treated with prophylactic cranial irradiation in the intervention group and all enrolled patients in the observation group). MMSE scores between the two groups at baseline, 12 months, and 24 months were compared according to the Wilcoxon test with data collected at each timepoint. All p values are reported as two-sided. All analyses were done by the West Japan Oncology Group Data Center with SAS software (version 9.1.3).

Two interim analyses were planned; adjustment for multiple comparisons was taken into account by the method of DeMets and Lan.[9] Multiplicity for analyses of the primary endpoint was adjusted with the O'Brien-Fleming type α-spending function. The first interim analysis was designed to judge the validity of continuing enrolment during the period of enrolment, and performed on the basis of data secured by the time half of the planned number of participants had been enrolled. Superiority of overall survival in the prophylactic cranial irradiation group would be demonstrated if overall survival in this group exceeded that in the observation group and the p value of the log-rank test with stratification according to age and ECOG performance status was less than the significance level determined by the α-spending function. We also examined whether the study should be terminated from clinical and statistical viewpoints (Bayesian predictive power) when the superiority of prophylactic cranial irradiation seemed very unlikely to be verified. The aim of the second interim analysis was to decide whether the preplanned follow-up was necessary. The second interim analysis was scheduled to be done with data collected at the time of completion of the protocol treatment in all enrolled participants. The results of these interim analyses

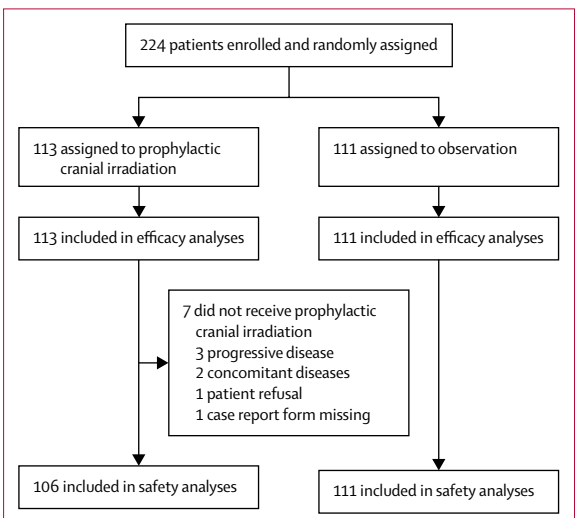

Figure 1: **Trial profile**

	Prophylactic cranial irradiation (n=113)	Observation (n=111)
Age (years)	69 (43–83)	69 (37–86)
≥70	53 (47%)	51 (46%)
<70	60 (53%)	60 (54%)
Sex		
Male	95 (84%)	98 (88%)
Female	18 (16%)	13 (12%)
ECOG performance status		
0–1	108 (96%)	107 (96%)
2	5 (4%)	4 (4%)
Response to initial chemotherapy		
Complete	17 (15%)	16 (14%)
Partial	95 (84%)	93 (84%)
Minor	1 (<1%)	2 (2%)
Total number of cycles of initial chemotherapy		
Three	1 (<1%)	3 (3%)
Four	96 (85%)	93 (84%)
Five	1 (<1%)	2 (2%)
Six	15 (13%)	12 (11%)
Seven	0	1 (<1%)
Regimen of initial chemotherapy		
Carboplatin plus etoposide	38 (34%)	47 (42%)
Cisplatin plus irinotecan	40 (35%)	32 (29%)
Cisplatin plus etoposide	21 (19%)	19 (17%)
Other*	14 (12%)	13 (12%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. *Most frequent other regimen was carboplatin plus irinotecan, three (3%) in prophylactic cranial irradiation group and three (3%) in the observation group; all other regimens were platinum containing.

Table 1: **Baseline characteristics**

would be reviewed by an independent data and safety monitoring committee. This trial is registered with the UMIN Clinical Trials Registry, number UMIN000001755.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 3, 2009, and July 17, 2013, 224 patients were enrolled and randomly assigned. The first planned interim analysis included the first 163 patients enrolled between April 3, 2009, and July 13, 2012. 165 patients (half the planned number of 330 patients) were enrolled but because the case report forms for two patients had not been submitted by the time of analysis, the analysed population consisted of 163 patients (84 in the prophylactic cranial irradiation group and 79 in the observation group); this analysis was done in July, 2013 (appendix p 4). As of the data cutoff on Oct 31, 2012, median follow-up for the 52 censored patients was 11·3 months (IQR 8·8–18·4; 11·2 months [8·7–20·2] in the prophylactic cranial irradiation group and 12·0 months [8·8–17·7] in the observation group). Baseline characteristics of the 163 patients were well balanced between the groups (appendix p 5). By the data cutoff point, 61 (73%) of 84 patients in the prophylactic cranial irradiation group and 50 (63%) of 79 in the observation group had died. Median overall survival was 10·1 months (95% CI 8·5–13·2) in the prophylactic cranial irradiation group and 15·1 months (10·2–18·7) in the observation group (HR 1·38, 95% CI 0·95–2·02; two-sided p=0·091; appendix p 6). The Bayesian predictive probability that prophylactic cranial irradiation would be shown to be significantly superior to observation by the end of this trial was 0·011%. Therefore, after discussion with the independent data and safety monitoring committee, this study was terminated early because of futility on July 17, 2013.

The final analysis included 224 patients enrolled and randomly assigned (113 to prophylactic cranial irradiation and 111 to observation; figure 1). Participants' baseline characteristics, including initial chemotherapeutic regimens before enrolment and response to initial chemotherapy, were well balanced between the two groups (table 1). Six patients who had been allocated to the prophylactic cranial irradiation group did not have the procedure, three because of rapid progressive disease before the procedure could be commenced (appendix p 7), two because of exacerbation of concomitant diseases (serious ventricular arrhythmia, dermatomyositis), and one because of patient refusal. The case report form of prophylactic cranial irradiation toxicity for one patient had not been submitted by the time of final analysis (figure 1). Thus, 106 patients in the prophylactic cranial irradiation group and 111 in the observation group were included in the analysis of adverse events. The median interval from the start of the previous cycle of chemotherapy to enrolment was 26 days (IQR 21–33), and to the start of prophylactic cranial irradiation was 37 days (30·25–44).

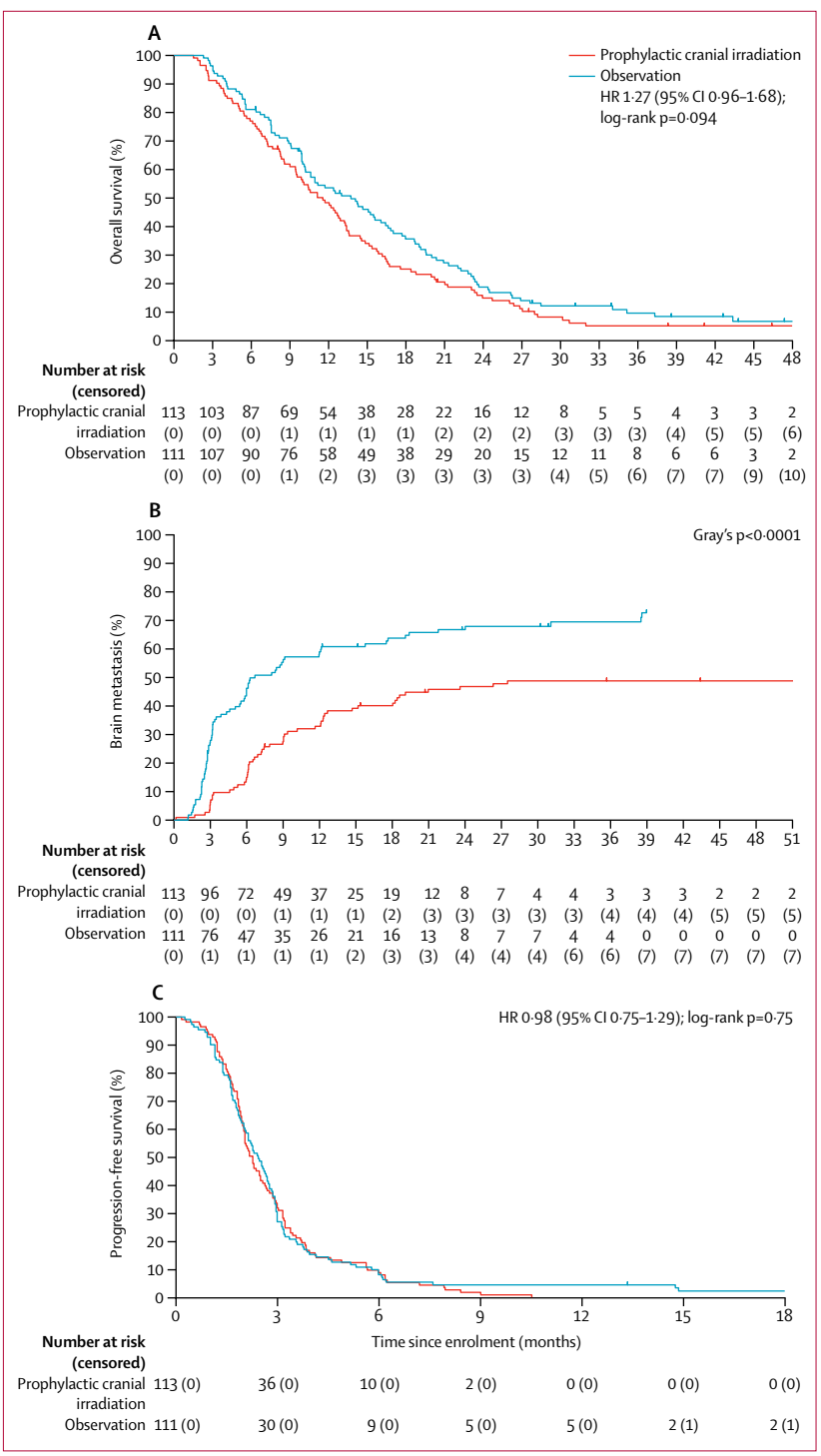

Figure 2: **Overall survival (A), cumulative incidence of brain metastases (B), and progression-free survival (C)**
HR=hazard ratio.

At the time of data cutoff (July 21, 2015), median follow-up of the 224 patients in the intention-to-treat population was 11·9 months (IQR 6·8–20·1). Median follow-up of the seven censored patients in the prophylactic cranial irradiation group was 38·3 months (IQR 20·5–46·5) and of the 12 censored patients in the observation group was 36·3 months (20·3–45·6).

106 patients in the prophylactic cranial irradiation group were irradiated with 25 Gy administered in ten fractions (median duration of prophylactic cranial irradiation 14 days [range 12–23]). Only five patients had 1–6 days of interruptions in their scheduled prophylactic cranial irradiation, all for personal reasons.

By the data cutoff point, 106 (94%) of 113 patients in the prophylactic cranial irradiation group and 99 (89%) of 111 in the observation group had died. 195 patients had died from progression of small-cell lung cancer (104 in the prophylactic cranial irradiation group *vs* 91 in the observation group), three from infection (two *vs* one), two from pneumonia (none *vs* two), two from unexplained sudden death (none *vs* two), one from cerebral haemorrhage (none *vs* one), and two from unspecified causes (none *vs* two). No significant difference between groups in overall survival was seen: median overall survival was 11·6 months (95% CI 9·5–13·3) in the prophylactic cranial irradiation group and 13·7 months (10·2–16·4) in the observation group (HR 1·27, 95% CI 0·96–1·68; two-sided log rank p=0·094; figure 2). Survival was 48·4% (95% CI 38·9–57·3) at 1 year and 15·0% (9·1–22·3) at 2 years in the prophylactic cranial irradiation group and 53·6% (43·8–62·4) at 1 year and 18·8% (12·0–26·7) at 2 years in the observation group.

Across the whole study, brain metastases were recorded in 54 (48%) of 113 patients in the prophylactic cranial irradiation group and in 77 (69%) of 111 patients in the observation group. The cumulative incidences of brain metastases at 6, 12, and 18 months were 15·0% (95% CI 9·2–22·3), 32·9% (24·3–41·7), and 40·1% (31·0–49·1), respectively, in the prophylactic cranial irradiation group and 46·2% (36·7–55·2), 59·0% (49·1–67·6), and 63·8% (54·0–72·1), respectively, in the observation group (Gray's p<0·0001; figure 2).

Progression-free survival did not differ significantly between the two groups: median progression-free survival was 2·3 months (95% CI 2·0–2·6) in the prophylactic cranial irradiation group versus 2·4 months (2·1–2·7) in the observation group (HR 0·98 [95% CI 0·75–1·29]; log rank p=0·75; figure 2).

Adverse events at 3 months after randomisation are shown in table 2. The most frequent grade 3 or worse adverse events at this timepoint were anorexia (six [6%] of 106 in the prophylactic cranial irradiation group *vs* two [2%] of 111 in the observation group), malaise (three [3%] *vs* one [<1%]), and muscle weakness in a lower limb (one [<1%] *vs* six [5%]). Cumulative adverse events recorded throughout the course of the follow-up period are shown in the appendix (p 8). No treatment-related deaths occurred in either group.

In this analysis, compliance with MMSE assessment was 212 (95%) patients at baseline (107 in the prophylactic cranial irradiation group *vs* 105 in the observation group), 83 (37%) at 12 months (37 *vs* 46), and 13 (6%) at 24 months (five *vs* eight). MMSE scores did not differ significantly between the two groups at baseline, 12 months, or 24 months according to the Wilcoxon test (figure 3).

Radiotherapy for brain metastases was given to 25 (46%) of 54 patients with brain metastases in the prophylactic cranial irradiation group and 64 (83%) of 77 patients with brain metastases in the observation group (table 3). The median interval from study enrolment to radiotherapy for brain metastases was 384 days (range 31–849; IQR 189–523) in the prophylactic cranial irradiation group and 193 days (38–1192; 104–349) in the observation group. Second-line chemotherapy was given to 99 (88%) patients in the prophylactic cranial irradiation group and 99 (89%) patients in the observation group (table 3).

Discussion

By contrast with findings from a previous study by the EORTC,[3] in this randomised, phase 3 study of patients

	Prophylactic cranial irradiation (n=106)				Observation (n=111)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	21 (20%)	24 (23%)	0	0	24 (22%)	16 (14%)	0	0
Dermatitis	17 (16%)	3 (3%)	1 (<1%)	1 (<1%)	3 (3%)	0	0	0
Headache	7 (7%)	0	0	0	3 (3%)	0	0	0
Anorexia	33 (31%)	10 (9%)	5 (5%)	1 (<1%)	14 (13%)	5 (5%)	2 (2%)	0
Nausea	25 (24%)	6 (6%)	2 (2%)	0	8 (7%)	1 (<1%)	0	0
Vomiting	7 (7%)	1 (<1%)	0	0	0	1 (<1%)	0	0
Dizziness	5 (5%)	2 (2%)	1 (<1%)	0	3 (3%)	0	0	0
Malaise	28 (26%)	7 (7%)	3 (3%)	0	21 (19%)	3 (3%)	0	1 (<1%)
Lethargy	6 (6%)	1 (<1%)	1 (<1%)	0	2 (2%)	1 (<1%)	0	0
Muscle weakness (lower limb)	3 (3%)	3 (3%)	1 (<1%)	0	1 (<1%)	0	5 (5%)	1 (<1%)

Table 2: **Adverse events at 3 months after randomisation**

with extensive-disease small-cell lung cancer, prophylactic cranial irradiation did not increase overall survival compared with that in patients who did not receive prophylactic cranial irradiation. There are several possible explanations for the discrepancy between the results of the EORTC study and our study. One important difference is that patients with extensive-disease small-cell lung cancer were enrolled in our study only after they had been confirmed not to have brain metastases by MRI before randomisation. By contrast, in the EORTC study only 29% of randomised patients had brain imaging at diagnosis,[10] and the proportion of patients who had brain imaging just before randomisation was not stated. There is no doubt that prophylactic cranial irradiation brings a substantial reduction in the incidence of brain metastases whether or not MRI screening is done before treatment. In a previous study, 17 (15%) of 112 patients with small-cell lung cancer had asymptomatic brain metastases on MRI at diagnosis.[4] In another study, investigators reported that 24 (13%) of 181 consecutive patients with small-cell lung cancer had asymptomatic brain metastases on MRI at diagnosis; asymptomatic brain metastases responded to systemic chemotherapy in only 27% of patients, which was much lower than the proportion of patients with a systemic response (73%).[11] Furthermore, despite this low response in the brain, a substantial number of patients who had asymptomatic brain metastases at initial diagnosis were still asymptomatic after completion of chemotherapy.[11] Thus, in the EORTC study, in which brain imaging was not part of standard staging and follow-up procedures unless symptoms suggestive of brain metastases were present, some randomised patients probably had asymptomatic brain metastases before randomisation. This speculation is supported by a report that asymptomatic brain metastases were identified by MRI before prophylactic cranial irradiation in as many as 13 (33%) of 40 patients with initial limited-disease small-cell lung cancer who had achieved complete response to chemoradiotherapy.[12] Thus, the longer overall survival reported by the EORTC study for patients who received prophylactic cranial irradiation might have reflected responses of asymptomatic brain metastases that had already been present before randomisation.

Although the incidence of brain metastases was higher in the observation group than in the prophylactic cranial irradiation group in our trial, this did not result in shorter survival in the observation group, by contrast with the EORTC study. This difference might be attributable to a difference in the proportion of patients who received subsequent treatment. Second-line chemotherapy was given to 88% of patients in the prophylactic cranial irradiation group and to 89% of patients in the observation group, and a greater proportion of patients in the observation group received third-line or fourth-line chemotherapy than did those in the prophylactic cranial irradiation group. In the EORTC study, prophylactic cranial irradiation had an adverse effect on appetite, nausea, and vomiting at 6 weeks or 3 months after the procedure;[13] the frequency and severity of anorexia, nausea, and malaise were also higher in the prophylactic cranial irradiation group than in the observation group at 3 months after randomisation in our study. Furthermore, 12·5% more patients in the prophylactic cranial irradiation group of the EORTC study than in the control group had severe worsening (>20 points) in global health status between baseline and 3 months.[13] In our study, anorexia, nausea, and malaise, which could be caused by chemotherapy, were frequent and severe in patients in the prophylactic cranial irradiation group beyond 3 months after randomisation.

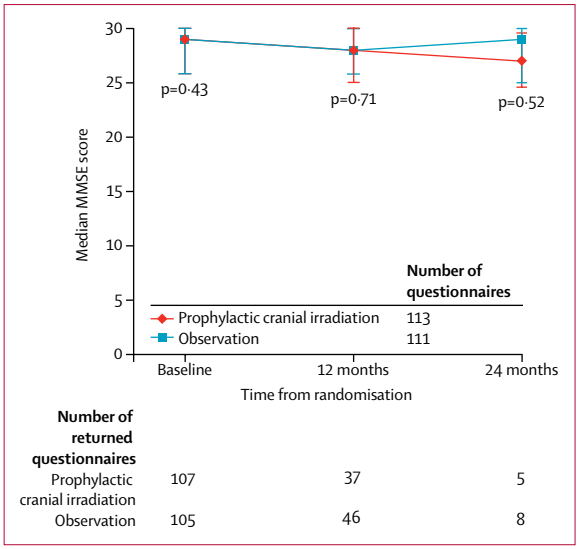

Figure 3: **Median scores for MMSE**
Error bars show IQR. MMSE=mini mental state examination.

	Prophylactic cranial irradiation (n=113)	Observation (n=111)
Radiotherapy for brain metastases	25 (46%)*	64 (83%)*
Second-line chemotherapy	99 (88%)	99 (89%)
Single agents	69 (61%)	67 (60%)
Platinum-based doublet	24 (21%)	28 (25%)
Other	6 (5%)	4 (4%)
Third-line chemotherapy	56 (50%)	68 (61%)
Single agents	38 (34%)	47 (42%)
Platinum-based doublet	15 (13%)	16 (14%)
Other	3 (3%)	5 (5%)
Fourth-line chemotherapy	29 (26%)	40 (36%)
Single agents	16 (14%)	27 (24%)
Platinum-based doublet	13 (12%)	12 (11%)
Other	0	1 (<1%)

Data are n (%). *Denominator is number of patients with brain metastases during follow-up (prophylactic cranial irradiation, n=54; observation, n=77).

Table 3: **Post-study treatment**

The persistence of these adverse events, and the resultant impairment in quality of life during subsequent chemotherapy, might have decreased the feasibility and tolerability of such treatment in the prophylactic cranial irradiation group in our study. Overall survival in our prophylactic cranial irradiation group was not longer than that in the observation group probably because of this decreased feasibility and tolerability.

MRI has been shown to be a more sensitive diagnostic technique than CT for detecting brain metastases[14,15] and is therefore widely recognised as the best means of identifying brain metastases before choosing the optimal therapeutic approach. As of 2011, there were roughly 47 MRI units per 1 million people in Japan; this is the largest ratio in the world.[16] In view of the high sensitivity with which MRI detects brain metastases and the easy accessibility to MRI in our country, our study protocol specified that all patients, irrespective of the presence or absence of neurological symptoms, underwent brain MRI at 3-month intervals up to 12 months and at 18 and 24 months after randomisation. At 12 months, brain metastases were diagnosed in 32·9% of patients in the prophylactic cranial irradiation group and in 59·0% of patients in the observation group, whereas in the EORTC study, symptomatic brain metastases were reported in 14·6% of patients in the prophylactic cranial irradiation group and in 40·4% of patients in the control group at 12 months. We believe that the higher frequency of brain metastases seen in our study is mainly attributable to the detection of asymptomatic brain metastases by MRI. In the EORTC study, more patients in the prophylactic cranial irradiation group were treated for progression than were patients in the control group (68·0% *vs* 45·1%).[3] By contrast, radiotherapy for brain metastases was given to 83% of patients in our observation group, compared with 59·3% in the EORTC study,[3] and a greater proportion of patients in both groups in our trial had subsequent chemotherapy than did patients in the EORTC study. The difference in the proportions of patients who had subsequent therapy between the two studies is presumably because some patients with symptomatic brain metastases in the control group of the EORTC study would not have had subsequent brain irradiation or chemotherapy because of deterioration in their general condition, whereas patients with asymptomatic brain metastases detected by MRI in our study did receive both radiotherapy and subsequent chemotherapy.

A pooled analysis of the Radiation Therapy Oncology Group (RTOG) randomised trials 0212 and 0214 has shown that prophylactic cranial irradiation is associated with a higher rate of decline in self-reported cognitive functioning compared with that for patients who received observation alone.[17] In our study, MMSE scores did not differ significantly between the two groups. However, because of the findings of the pooled analysis, the indication for prophylactic cranial irradiation in patients with extensive-disease small-cell lung cancer with a confirmed absence of brain metastases should be judged carefully because of the risk of declining cognitive function.

Meta-analyses[1,2] have shown that prophylactic cranial irradiation adds a survival benefit to initial therapy in patients with extensive-disease small-cell lung cancer who achieve a complete response. A survival benefit for patients with a complete response has been reported in previous trials in which CT was used to detect brain metastases.[18–20] Some of the patients enrolled in these studies could have had asymptomatic brain metastases. We therefore consider that the results of these previous studies on prophylactic cranial irradiation in patients with extensive-disease small-cell lung cancer who achieved a complete response cannot be extrapolated to the current clinical situation in which MRI is in widespread use for detection of brain metastases.

One limitation of our study was the absence of neurocognitive and functional assessment other than MMSE. Such assessments would have been informative to aid understanding of why prophylactic cranial irradiation did not add survival benefit in our study. Another limitation was that our study was done only in Japan, where there is easy access to MRI. Whether there are ethnic differences in the effects of radiotherapy on brain metastases between Japanese and non-Japanese patients is uncertain. However, ethnic differences in the response and adverse events to chemotherapeutic drugs do exist between these populations. In addition to the differences in study design, there could be a possibility that ethnicities affect the results of the two studies from Japan and Europe. Thus, the results of our study might not change routine practice in different medical situations. Finally, absence of cost-effectiveness analysis of frequent MRI imaging during follow-up and subsequent treatment of asymptomatic brain metastases was a weakness of our study. All patients, irrespective of the presence or absence of neurological symptoms, were required to have several brain MRIs after enrolment. Radiotherapy for brain metastases was given to 64 (58%) of 111 patients in the observation group and 25 (22%) of 113 patients in the prophylactic cranial irradiation group. If the cost of the observation strategy (MRI plus radiotherapy for brain metastases) is lower than that of prophylactic cranial irradiation (prophylactic cranial irradiation plus MRI plus radiotherapy for brain metastases), the observation strategy could be recommended because of the equal survival.

On the basis of the results of this Japanese trial, we conclude that prophylactic cranial irradiation is not essential for patients with extensive-disease small-cell lung cancer with any response to initial chemotherapy and a confirmed absence of brain metastases by MRI when patients are periodically assessed by MRI examination during follow-up and asymptomatic metastases are treated. However, physicians in countries other than Japan should be cautious when extrapolating the results of this study to general practice in view of different ethnicities and medical situations.

Contributors

All authors were involved in the conception and design of the study, and the provision of study material, patients, and data acquisition. TT, TY, TS, and NY were responsible for data management, statistical analysis, and data interpretation. All authors were involved in writing the report and approved the final version.

Declaration of interests

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