PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

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ABSTRACT

Background Prophylactic cranial irradiation reduces the incidence of brain metastasis in patients with small-cell lung cancer. Whether this treatment, when given to patients in complete remission, improves survival is not known. We performed a meta-analysis to determine whether prophylactic cranial irradiation prolongs survival.

Methods We analyzed individual data on 987 patients with small-cell lung cancer in complete remission who took part in seven trials that compared prophylactic cranial irradiation with no prophylactic cranial irradiation. The main end point was survival.

Results The relative risk of death in the treatment group as compared with the control group was 0.84 (95 percent confidence interval, 0.73 to 0.97; P= 0.01), which corresponds to a 5.4 percent increase in the rate of survival at three years (15.3 percent in the control group vs. 20.7 percent in the treatment group). Prophylactic cranial irradiation also increased the rate of disease-free survival (relative risk of recurrence or death, 0.75; 95 percent confidence interval, 0.65 to 0.86; P<0.001) and decreased the cumulative incidence of brain metastasis (relative risk, 0.46; 95 percent confidence interval, 0.38 to 0.57; P<0.001). Larger doses of radiation led to greater decreases in the risk of brain metastasis, according to an analysis of four total doses (8 Gy, 24 to 25 Gy, 30 Gy, and 36 to 40 Gy) (P for trend=0.02), but the effect on survival did not differ significantly according to the dose. We also identified a trend (P=0.01) toward a decrease in the risk of brain metastasis with earlier administration of cranial irradiation after the initiation of induction chemotherapy.

Conclusions Prophylactic cranial irradiation improves both overall survival and disease-free survival among patients with small-cell lung cancer in complete remission. (N Engl J Med 1999;341:476-84.)

IN patients with limited small-cell lung cancer, chemotherapy combined with thoracic radiotherapy yields complete response rates of 50 to 85 percent, a median duration of survival of 12 to 20 months, and 2-year disease-free survival rates of 15 to 40 percent.[1-3] Five-year survival rates may exceed 20 percent for patients who have complete responses.[3] With the combined treatment, the risk of a thoracic recurrence decreases, and as a result, brain metastasis becomes one of the main types of relapse. Although only 10 percent of patients have brain metastasis at the time of diagnosis, the cumulative incidence at two years is more than 50 percent,[4,5] which is consistent with the rate found in autopsy series.[6]

In the early 1970s, the brain was assumed to be a pharmacologic sanctuary where subclinical metastases were protected from cytotoxic drugs by the blood–brain barrier,[7] and it was suggested that cranial irradiation might prevent the development of clinically evident brain metastases. These hypotheses led to several clinical trials that evaluated the role of prophylactic cranial irradiation in patients with small-cell lung cancer. In early small trials, there was a decrease in the rate of brain metastasis but no improvement in survival.[8] A review of retrospective data suggested that any prolongation of survival would be restricted to patients in complete remission, because those with residual extracranial cancer die of systemic cancer.[9]

Starting in the early 1980s, some investigators reported possible toxic effects of irradiation on neuropsychological functions,[10-14] usually in patients who had received potentially neurotoxic drugs concurrently with prophylactic cranial irradiation. Subsequently, trials comparing prophylactic cranial irradiation with no cranial irradiation were conducted in patients in complete remission, and some of the trials included neuropsychological assessment. The results of these trials consistently revealed a significant decrease in the incidence of brain metastasis with no increase in neuropsychological complications.[5,15] The results, however, remained inconclusive with regard to the benefit in terms of overall survival. The Prophylactic Cranial Irradiation Overview Collaborative Group was therefore created to undertake a meta-analysis based on data on individual patients in order

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to determine whether prophylactic cranial irradiation might lead to a moderate improvement in survival.

METHODS

Inclusion Criteria

Trials that were eligible for inclusion in the meta-analysis were those in which patients with small-cell lung cancer in complete remission were randomly assigned to receive prophylactic cranial irradiation (the treatment group) or no prophylactic cranial irradiation (the control group). The trials had to have included only patients with histologically proved small-cell lung cancer who had a complete response after induction chemotherapy with no evidence of brain metastasis before randomization and no previous cranial irradiation. Enrollment had to have been completed between January 1965 and December 1995.

Methods of Searching for Trials

The meta-analysis aimed to include both published and unpublished trials. To identify potentially eligible trials, we searched electronic data bases (Medline, CancerLit, Excerpta Medica, and Biosis), reference lists of published reports of trials, review articles, and relevant books. The search was also guided by discussions with investigators and by the examination of proceedings of meetings (the American Society of Clinical Oncology and the International Association for the Study of Lung Cancer) and the Physician Data Query registry of clinical trials.

Data on Individual Patients

We collected data on individual patients from the principal investigators for all patients randomly assigned to a treatment group, including those who had been excluded from the investigators' analyses. The following data were requested: patient identifiers; sex; age; performance status at the time of randomization; initial stage of disease; details of induction therapy that led to a complete response; starting date of induction therapy; date of randomization; treatment assigned; and updated information on survival, brain metastases, other metastases, and local or regional recurrence. Data were checked for internal consistency and for consistency with published results and were amended as necessary on the basis of correspondence with the investigators.

End Points

The main end point was overall survival, defined as the time from randomization to death from any cause. Secondary end points were disease-free survival (time from randomization to a first event, either death or relapse), the cumulative incidence of brain metastasis, the cumulative incidence of other metastases, and the cumulative incidence of local or regional recurrence (for this analysis, data on patients who died without the event under consideration were censored as of the date of death).

Statistical Analysis

All analyses were carried out on an intention-to-treat basis; that is, all patients randomly assigned to a treatment group were included in the analyses according to the assigned treatment, irrespective of whether they received the treatment or were excluded from analysis by the investigators. Follow-up was quantified by the reverse Kaplan–Meier method.[16]

The statistical method used has been described elsewhere.[17] Analyses were performed with the log-rank test with adjustment for the trial. In each trial, the number of deaths observed (O) among patients assigned to treatment was compared with the number of deaths expected (E), on the assumption that the prob-

TABLE 1. CHARACTERISTICS OF THE SEVEN TRIALS INCLUDED IN THE META-ANALYSIS.*

TRIAL	ENROLLMENT PERIOD	MEDIAN FOLLOW-UP	INDUCTION THERAPY	TOTAL DOSE/ NO. OF FRACTIONS (DOSE/FRACTION)	MEDIAN TIME BETWEEN START OF INDUCTION THERAPY AND ENROLLMENT	NO. OF PATIENTS	NO. OF PATIENTS SURVIVING
		yr			mo		
UMCC[29]	1977–1980	18.5	CT	30 Gy/10 (3 Gy)	3.6	29	2
Okayama[30]	1981–1986	11.7	CT or CT plus RT	40 Gy/20 (2 Gy)	2.5	46	4
PCI-85[5]	1985–1993	8.4	CT or CT plus RT	24 Gy/8 (3 Gy)	5.3	300	32
Danish–NCI (unpublished)	1985–1991	8.8	CT	24 Gy/8 (3 Gy)	4.4	55	7
UKCCCR–EORTC[15]	1987–1995	3.5	CT or CT plus RT	8–36 Gy/1–18†	NA	314	54
PCI-88[31]	1988–1994	5.1	CT or CT plus RT	24 Gy/8 (3 Gy)	5.1	211	37
ECOG–RTOG[32]	1991–1994	3.9	CT or CT plus RT	25 Gy/10 (2.5 Gy)	NA	32	5

*UMCC denotes University of Maryland Cancer Center, CT chemotherapy, RT thoracic radiotherapy, PCI-85 the Prophylactic Cranial Irradiation trial started in 1985, NCI National Cancer Institute, UKCCCR–EORTC United Kingdom Coordinating Committee for Cancer Research–European Organisation for Research and Treatment of Cancer, NA not available, PCI-88 the Prophylactic Cranial Irradiation trial started in 1988, and ECOG–RTOG Eastern Cooperative Oncology Group–Radiation Therapy Oncology Group.

†During the first period of the trial, there were three treatment groups: no prophylactic cranial irradiation, prophylactic cranial irradiation at a total dose of 24 Gy in 12 fractions, and prophylactic cranial irradiation at a total dose of 36 Gy in 18 fractions. During the second period of the trial, there were only two treatment groups: no prophylactic cranial irradiation and prophylactic cranial irradiation at various doses.

ability of death was unrelated to treatment. The values for O minus E and for its variance (V) were summed over the whole set of trials to obtain a grand total (GT) and a total variance (V_T). The ratio GT: $\sqrt{V_T}$, or z, tests the effect of treatment for statistical significance. The Cox proportional-hazards analysis, stratified according to trial, was used to adjust the analyses for the covariables.

For each trial, the relative risk of death in the treatment group, as compared with the control group, was estimated as the hazard ratio, or exponential $[(O-E)\div V]$. The pooled relative risk was estimated as exponential $[GT\div V_T]$, with a 95 percent confidence interval estimated as exponential $[GT\div V_T \pm 1.96\div \sqrt{V_T}]$. The percentage reduction in the risk of death was estimated as 100 [1−relative risk] and indicates the proportional reduction in mortality resulting from treatment. Chi-square tests for heterogeneity were used to test for statistical heterogeneity among trials. We calculated the absolute difference in the three-year survival rate, using the pooled relative risk and the survival rate in the control group; proportional hazards were assumed.[18] Crude Kaplan–Meier survival curves (i.e., curves not stratified according to trial) were plotted. The same analyses were performed for the other end points.

We made an indirect comparison of the trials according to the total dose of prophylactic cranial irradiation (categorized arbitrarily as 8 Gy, 24 to 25 Gy, 30 Gy, and 36 to 40 Gy) through a test for trend that took into account the four dose categories.[17] Subgroup analyses were performed according to sex, age, performance status, initial stage of disease, type of induction therapy, and time between the initiation of induction therapy and randomization. All statistical tests were two-tailed.

RESULTS

Trials

We identified 17 trials, including 1 unpublished trial (the Danish–National Cancer Institute [NCI] trial), in which patients with small-cell lung cancer were randomly assigned to receive prophylactic cranial irradiation or no treatment.[5,15,19-32] Ten trials, involving a total of 929 patients, were excluded from the analysis for one or more of the following reasons: the patients were randomly assigned to receive radiation therapy before the response to induction therapy was evaluated[19-28]; the comparison group received mannitol rather than no treatment[24]; the method of randomization was inadequate[21]; and patients with inoperable carcinoma of the lung, who had not been stratified according to histologic diagnosis, were included.[20] Thus, the results are based on seven trials, or 987 patients[5,15,29-32] (and Danish–NCI trial: unpublished data). Most patients were enrolled after 1985. The analysis of survival was based on all 987 patients. Only eight patients had been excluded from the investigators' original analyses: six patients had brain metastasis at enrollment, one was not in complete remission, and one refused irradiation after enrollment.

The characteristics of the seven trials are shown in Table 1. Four trials were small, with 55 or fewer patients. The remaining three trials involved 825 patients, or 84 percent of all patients. The Prophylactic Cranial Irradiation trial started in 1988 (PCI-88),[31] which did not include neuropsychological assessment, was a simplified trial conducted in parallel with a trial started in 1985 (PCI-85).[5] The policy to determine complete remission differed in each trial; some trials required a simple chest film, and others required bronchoscopy or computed tomography (CT) of the chest or brain. In all trials except for the United Kingdom Coordinating Committee for Cancer Research–European Organisation for Research and Treatment of Cancer (UKCCCR–EORTC) trial,[15] the recommended dose of cranial irradiation ranged from 24 to 40 Gy given in 8 to 20 fractions, which corresponds to a dose of 2 to 3 Gy per fraction. The UKCCCR–EORTC trial had two randomization periods. During the first, patients were randomly assigned to three treatment groups: a control group, a group receiving prophylactic cranial irradiation at 24 Gy in 12 fractions, and a group receiving irradiation at 36 Gy in 18 fractions. During the second period, there were only two treatment groups, with a randomization ratio of 2 to 3: a control group and a group receiving prophylactic cranial irradiation. The recommended total dose was between 20 and 36 Gy, but the choice was left to in-

TABLE 2. CHARACTERISTICS OF THE 987 PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION.

CHARACTERISTIC	GROUP TREATED WITH PROPHYLACTIC CRANIAL IRRADIATION (N=526)	CONTROL GROUP (N=461)
Male sex — no. (%)	403 (77)	352 (76)
Age		
Median — yr	59	59
Range — yr	26–80	21–79
<55 yr — no. (%)	147 (28)	158 (34)
55–64 yr — no. (%)	250 (48)	185 (40)
≥65 yr — no. (%)	129 (25)	118 (26)
Performance status — no. (%)*		
0	212 (67)	215 (66)
1	96 (30)	105 (32)
2–3	7 (2)	6 (2)
Extensive initial disease — no. (%)†	62 (12)	78 (17)
Induction treatment with chemotherapy plus thoracic radiotherapy — no. (%)‡	314 (77)	248 (74)
Time between start of induction therapy and randomization — no. (%)§		
<4 mo	84 (27)	77 (24)
4–6 mo	127 (41)	152 (48)
>6 mo	102 (33)	91 (28)

*0 denotes asymptomatic, 1 symptomatic and fully ambulatory, 2 symptomatic and in bed less than 50 percent of the day, and 3 symptomatic and in bed 50 percent or more of the day. Data were not available for the 343 patients from the University of Maryland Cancer Center and United Kingdom Coordinating Committee for Cancer Research–European Organisation for Research and Treatment of Cancer trials and for 3 additional patients.

†Extensive initial disease was defined as disease extending beyond one hemithorax or beyond regional lymph nodes. P=0.02 by the chi-square test.

‡Data were not available for the 243 patients from the Prophylactic Cranial Irradiation trial started in 1988 and the Eastern Cooperative Oncology Group–Radiation Therapy Oncology Group trial and for 2 additional patients.

§Data were not available for the 346 patients from the United Kingdom Coordinating Committee for Cancer Research–European Organisation for Research and Treatment of Cancer and Eastern Cooperative Oncology Group–Radiation Therapy Oncology Group trials and for 8 additional patients.

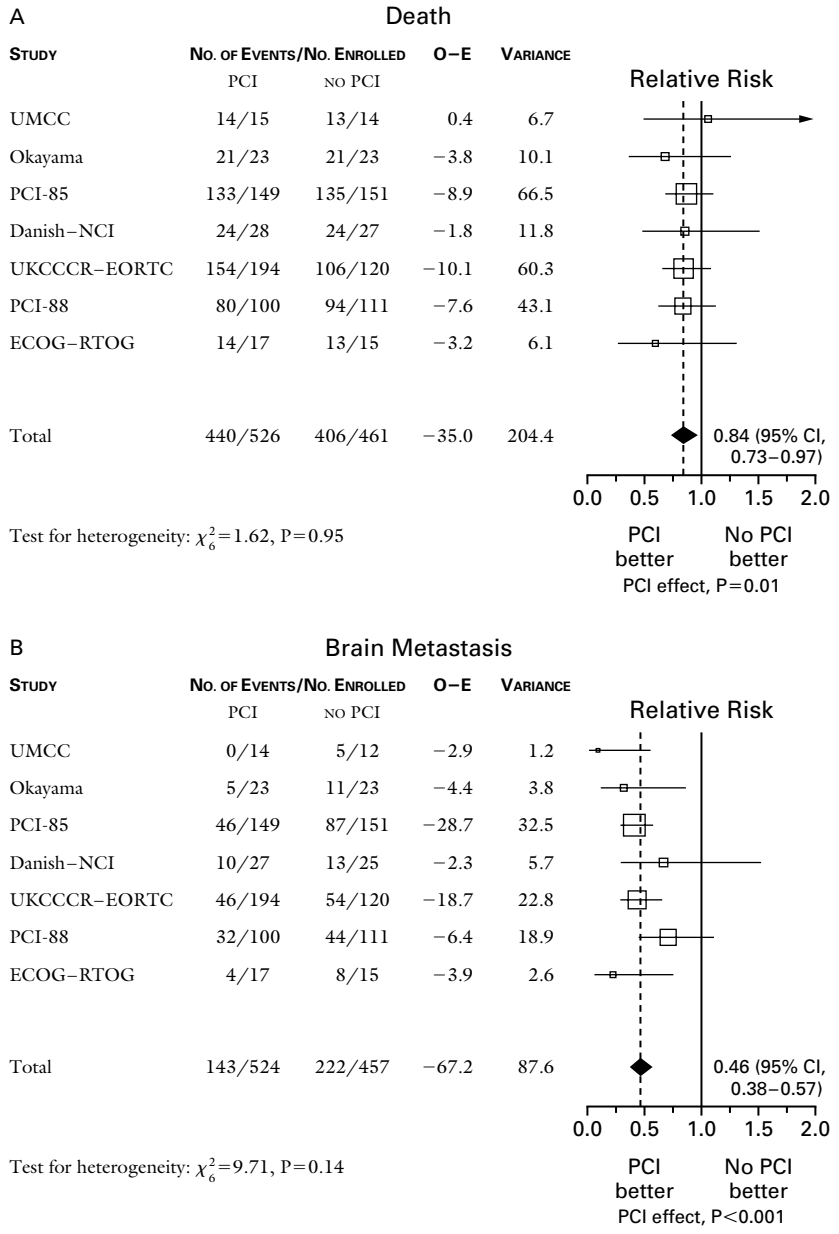

Figure 1. Relative-Risk Plots for Death (Panel A) and Brain Metastasis (Panel B) in Patients with Small-Cell Lung Cancer in Complete Remission, According to Whether They Were Assigned to Treatment with Prophylactic Cranial Irradiation (PCI).

The center of each square represents the relative risk for the individual trial, and each horizontal line its 95 percent confidence interval; the area of each square is proportional to the amount of information derived from the trial. The broken line and the center of each diamond represent the pooled relative risk, and the extremities of the diamond represent its 95 percent confidence interval. Brain-metastasis status was unknown for six patients; these patients were excluded from the analysis of brain metastasis. O denotes the number of deaths observed, E the number of deaths expected, UMCC University of Maryland Cancer Center, PCI-85 the Prophylactic Cranial Irradiation trial started in 1985, PCI-88 the Prophylactic Cranial Irradiation trial started in 1988, NCI National Cancer Institute, UKCCCR−EORTC United Kingdom Coordinating Committee for Cancer Research−European Organisation for Research and Treatment of Cancer, ECOG−RTOG Eastern Cooperative Oncology Group−Radiation Therapy Oncology Group, and CI confidence interval.

dividual centers, and one center chose 8 Gy in one fraction. Because 120 patients in this trial were randomly assigned to the control group and 194 to the treatment group, the overall numbers of patients in the two groups in the meta-analysis differ (461 in the control group vs. 526 in the treatment group).

The characteristics of the 987 patients are shown in Table 2. Because the UKCCCR–EORTC trial included only patients with limited disease and included more patients in the treatment group than in the control group, overall there were significantly more patients with extensive initial disease in the control group ($P=0.02$). This difference was no longer significant after adjustment for the trial.

Overall Survival

Eight hundred forty-six patients died. The length of the follow-up period did not differ significantly between the two groups: the median was 5.3 years in the control group and 5.9 years in the treatment group. The combined result revealed a significant ($P=0.01$) survival benefit in the group assigned to prophylactic cranial irradiation as compared with the control group, with a pooled relative risk of 0.84 (95 percent confidence interval, 0.73 to 0.97) (Fig. 1A and Table 3). The relative risk was similar after adjustment for the extent of disease, sex, and age (relative risk, 0.83; $P=0.009$). The results were also similar after additional adjustment for performance status, type of induction therapy, and time between the start of induction therapy and randomization. There was no evidence of heterogeneity among the trials. The result corresponded to a mean (±SD) reduction in the risk of death of 16±6 percent, and to an absolute increase in survival of 5.4 percent at three years after randomization, from 15.3 percent in the control group to 20.7 percent in the treatment group (Fig. 2A). The survival benefit persisted beyond three years.

Other End Points

Prophylactic cranial irradiation reduced the incidence of brain metastasis, with a pooled relative risk of 0.46 (95 percent confidence interval, 0.38 to 0.57; $P<0.001$) (Fig. 1B and Table 3). This result corresponded to a 54±7 percent reduction in the risk of brain metastasis and to an absolute decrease of 25.3 percent in the cumulative incidence of brain metastasis at three years, from 58.6 percent in the control group to 33.3 percent in the treatment group (Fig. 2B).

Data on the occurrence of metastases at other sites and on local or regional recurrences were available for only 67 percent of the patients. Prophylactic cranial irradiation significantly improved disease-free survival (relative risk, 0.75; 95 percent confidence interval, 0.65 to 0.86; $P<0.001$) but had no effect on other metastases or on local or regional recurrences. The results of analyses of the four secondary end points after adjustment for the covariables, particularly for the extent of disease, were similar.

Indirect Comparisons

We subdivided the trials into four categories according to radiation dose: 8 Gy in 1 fraction (UKCCCR–EORTC period 2, Christie Hospital), 24 to 25 Gy

TABLE 3. RESULTS OF THE META-ANALYSIS OF PROPHYLACTIC CRANIAL IRRADIATION IN PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION.*

END POINT	NO. OF PATIENTS		RELATIVE RISK (95% CI)	P VALUE	HETEROGENEITY (P VALUE)	RATE IN THE CONTROL GROUP OVER A 3-YR PERIOD	ABSOLUTE BENEFIT AT 3 YR
	TREATMENT GROUP	CONTROL GROUP					
						percent	
Overall survival	526	461	0.84 (0.73–0.97)	0.01	0.95	15.3	+5.4
Disease-free survival	526	461	0.75 (0.65–0.86)	<0.001	0.96	13.5	+8.8
Cumulative incidence of brain metastasis	524	457	0.46 (0.38–0.57)	<0.001	0.14	58.6	−25.3
Cumulative incidence of other metastases	325	332	0.89 (0.69–1.15)	0.37	0.51	45.6	−3.8
Cumulative incidence of local or regional recurrence	323	334	0.97 (0.75–1.26)	0.84	0.45	45.1	−1.0

*Brain-metastasis status was unknown for six patients, who were therefore excluded from the analysis of brain metastasis. The status with respect to other metastases and local and regional recurrence was unknown for 330 patients, who were therefore excluded from the analyses of these events. CI denotes confidence interval.

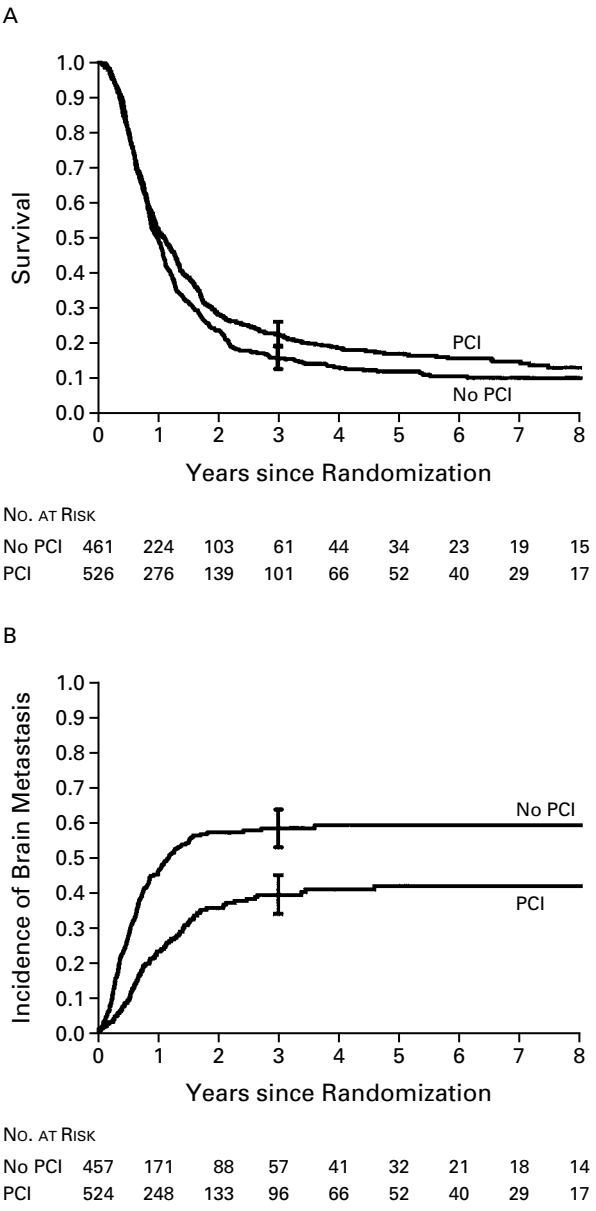

Figure 2. Kaplan–Meier Estimates of Survival (Panel A) and the Cumulative Incidence of Brain Metastasis (Panel B) in Patients with Small-Cell Lung Cancer in Complete Remission, According to Whether They Were Assigned to Treatment with Prophylactic Cranial Irradiation (PCI).

The I bars denote the 95 percent confidence intervals for the actuarial rates. The duration of survival and the occurrence of brain metastasis are described in terms of the period between randomization (a median of five months after the start of induction chemotherapy) and the follow-up assessment. Brain-metastasis status was unknown for six patients, who were therefore excluded from the analysis of brain metastasis. The relative risk of death in the group assigned to prophylactic cranial irradiation was 0.84 (95 percent confidence interval, 0.73 to 0.97), and the relative risk of brain metastasis in this group was 0.46 (95 percent confidence interval, 0.38 to 0.57), as compared with the control group.

in 8 to 12 fractions (UKCCCR–EORTC period 1, PCI-85, Danish–NCI, PCI-88, Eastern Cooperative Oncology Group–Radiation Therapy Oncology Group [ECOG–RTOG]), 30 Gy in 10 fractions (UKCCR–EORTC period 2, University of Maryland Cancer Center [UMCC]), and 36 or 40 Gy in 18 or 20 fractions (UKCCCR–EORTC period 1, Okayama). The effect of treatment on survival did not differ significantly according to the total dose ($P=0.89$). However, there was a significant trend ($P=0.02$) toward a lower risk of brain metastasis as the radiation dose increased (Table 4).

Subgroup Analyses

Data on predefined subgroups of patients were analyzed to determine whether the effect of treatment varied among subgroups. Data on sex, age, and extent of initial disease were available for all patients. Data on performance status, induction therapy, and time between the start of induction therapy and randomization were available for 641 patients (65 percent), 742 patients (75 percent), and 633 patients (64 percent), respectively. There was no evidence that any subgroup of patients benefited more or less from treatment, except in the subgroups defined according to sex and the interval between the initial induction therapy and randomization (Table 4). Prophylactic cranial irradiation reduced the risk of death for the 755 men (relative risk, 0.77), whereas it had no effect in the 232 women (relative risk, 1.05; $P=0.07$ for the comparison of the relative risks). The frequency of brain metastasis did not differ significantly ($P=0.87$) between women and men, but among women, the rate of other metastases was lower in the control group than in the treatment group (data not shown).

There was a significant trend ($P=0.01$) toward a greater effect of prophylactic cranial irradiation on the incidence of brain metastasis in patients randomized sooner after induction therapy than in those randomized later. However, the time between the initial treatment and randomization had no effect on the risk of death.

DISCUSSION

Our meta-analysis of seven trials that evaluated prophylactic cranial irradiation in 987 patients with small-cell lung cancer in complete remission showed that prophylactic cranial irradiation leads to a small but significant absolute reduction in mortality (5.4 percent), even after adjustment for the extent of initial disease. Irradiation not only significantly reduced the risk of brain metastasis, as previously shown in individual trials, but also improved overall and disease-free survival. These results confirm that prophylactic cranial irradiation prevents and does not simply delay the emergence of brain metastases. Because the examinations required to determine a complete response among the trials were heterogeneous, one

TABLE 4. INDIRECT AND SUBGROUP ANALYSES.*

CHARACTERISTIC	NO. OF PATIENTS		RELATIVE RISK OF DEATH (95% CI)	P VALUE		RELATIVE RISK OF BRAIN METASTASIS (95% CI)	P VALUE	
	TREATMENT GROUP (N=526)	CONTROL GROUP (N=461)		INTERACTION	TREND		INTERACTION	TREND
Total dose of cranial irradiation†				0.89	0.81		0.11	0.02
8 Gy	26	16	0.69 (0.35–1.37)			0.76 (0.28–2.10)		
24–25 Gy	330	340	0.88 (0.75–1.04)			0.52 (0.41–0.67)		
30 Gy	119	82	0.81 (0.59–1.12)			0.34 (0.19–0.59)		
36–40 Gy	51	59	0.81 (0.54–1.20)			0.27 (0.14–0.51)		
Sex				0.07			0.87	
Male	403	352	0.77 (0.66–0.90)			0.45 (0.36–0.58)		
Female	123	109	1.05 (0.78–1.42)			0.47 (0.31–0.74)		
Age				0.74	0.75		0.41	0.20
<55 yr	147	158	0.84 (0.65–1.02)			0.55 (0.39–0.77)		
55–64 yr	250	185	0.90 (0.73–1.11)			0.49 (0.35–0.68)		
≥65 yr	129	118	0.79 (0.60–1.03)			0.37 (0.24–0.59)		
Performance status‡				0.62			0.82	
0	212	215	0.85 (0.69–1.05)			0.47 (0.35–0.63)		
1–3	103	111	0.78 (0.58–1.04)			0.50 (0.32–0.78)		
Initial disease				0.62			0.42	
Limited	464	383	0.85 (0.73–0.99)			0.48 (0.38–0.60)		
Extensive	62	78	0.77 (0.54–1.11)			0.38 (0.23–0.64)		
Induction therapy§				0.88			0.76	
Chemotherapy plus thoracic radiotherapy	314	248	0.86 (0.71–1.03)			0.43 (0.33–0.57)		
Chemotherapy without thoracic radiotherapy	94	86	0.88 (0.64–1.21)			0.40 (0.23–0.67)		
Time between start of induction therapy and randomization¶				0.46	0.39		0.03	0.01
<4 mo	84	77	0.92 (0.66–1.29)			0.27 (0.16–0.46)		
4–6 mo	127	152	0.79 (0.61–1.02)			0.50 (0.35–0.72)		
>6 mo	102	91	1.01 (0.74–1.38)			0.69 (0.44–1.08)		

*CI denotes confidence interval.

†In one trial, with three treatment groups (one control group and two groups receiving different doses of radiation), the control group is counted twice.

‡Data were not available for 346 patients.

§Data were not available for 245 patients.

¶Data were not available for 354 patients.

can speculate that prophylactic cranial irradiation might also be beneficial in patients with a good partial response assessed with the diagnostic methods used today. The benefit was consistent among subgroups defined according to age, performance status, extent of initial disease, and type of induction therapy. However, in terms of survival, prophylactic cranial irradiation was less effective in women than in men. This result should be interpreted with caution, however, because it was from a subgroup analysis and because there was some heterogeneity among the women in the various trials. Although women have higher survival rates than men (data not shown), there is no hypothesis to explain this difference in effect.

In the 1980s, several nonrandomized studies found neuropsychological impairment and abnormalities on CT scans of the brain that were potentially related to prophylactic cranial irradiation,[10-14] and a recent study of patients treated by prophylactic cranial irradiation and concomitant chemotherapy suggested that this combination had a negative effect on cognitive function, which was assessed at the end of treatment.[33] However, many confounding factors, such as age, long-term tobacco use, paraneoplastic syndromes, micrometastases, and the neurotoxicity of anticancer drugs, may have effects erroneously attributed to irradiation.

Whether prophylactic cranial irradiation leads to neuropsychological sequelae could not be addressed in this meta-analysis, because neuropsychological evaluation was performed in only two of the trials.[5,15] The initial neuropsychological assessment, performed in 350 patients in these trials before enrollment, revealed that many patients in the two trials (24 to 60 percent) had abnormalities. The results of repeated tests during the first years of follow-up revealed that the changes in neuropsychological function and the frequency of abnormalities on CT scans of the

brain did not differ between the treated and untreated patients. These results should somewhat alleviate concern about neuropsychological sequelae of prophylactic cranial irradiation, but longer follow-up is needed.

In recent years, the duration of survival of patients with small-cell lung cancer has increased as more effective systemic chemotherapy has been combined with thoracic radiotherapy,[34-36] so the cumulative risk of brain metastasis has increased.[5,15,36] Because the mean duration of survival is brief (approximately 4.5 months) after brain metastases are detected, despite treatment with high-dose cranial irradiation,[5] the overriding objective is prevention. Moreover, one potential advantage of prophylactic cranial irradiation is an improved quality of life.[37]

The effect of prophylactic cranial irradiation on survival in this meta-analysis (an absolute improvement of 5.4 percent [from 15.3 percent in the control group to 20.7 percent in the treatment group at three years after enrollment]) is similar to that found previously for thoracic radiotherapy in patients with small-cell lung cancer (an increase in survival of 5.4 percent [from 8.9 percent to 14.3 percent at three years after the start of induction chemotherapy]).[34] Most of the patients in the studies included in the meta-analysis received thoracic radiotherapy. Because the effects of these two treatments are different, it is likely that their beneficial effects are additive.

The reduction in the risk of brain metastasis increased slightly with the total dose of radiation. A dose–response relation was found in a recent review[38]; higher doses were necessary when prophylactic cranial irradiation was delayed for more than 60 days after induction treatment had been initiated. In our study, there was a significant trend toward a greater reduction in the incidence of brain metastasis among patients who received prophylactic cranial irradiation earlier. Only one small trial has prospectively investigated the effect of the timing of prophylactic cranial irradiation. However, this factor was confounded by the timing of chemotherapy, and the study revealed no difference in the frequency of brain metastases according to whether prophylactic irradiation was delivered at the start of induction treatment or six weeks later.[39]

In conclusion, prophylactic cranial irradiation should now be considered part of the standard treatment of patients with small-cell lung cancer in complete remission. Establishing the optimal dose and timing of treatment so as to reduce further the incidence of brain metastases with minimal and acceptable toxicity should be the aim of future clinical trials.

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APPENDIX

The following trial groups and investigators collaborated in the meta-analysis: Danish–NCI trial — Bruce E. Johnson and Paul E.G. Kristjansen; ECOG–RTOG trial — Michael Jiroutek, Andrew T. Turrisi, and Henry Wagner; Okayama trial — Taisuke Ohonoshi and Hiroshi Ueoka; PCI-85 and PCI-88 trials — Rodrigo Arriagada, Simone Benhamou, Agnès Laplanche, Thierry Le Chevalier, and Michèle Tarayre; UKCCCR–EORTC trial — Anna Gregor and Richard J. Stephens; and UMCC trial — Joseph Aisner and Margaret Whitacre. Other participants were as follows: Secretariat and Writing Committee — Rodrigo Arriagada, Anne Aupérin, Cécile Le Péchoux, and Jean-Pierre Pignon (Institut Gustave-Roussy, Villejuif, France); Advisory Group to the Secretariat — Thierry Le Chevalier (Institut Gustave-Roussy, Villejuif, France), Robert L. Souhami (University College London Medical School, London), and Lesley A. Stewart (Medical Research Council Cancer Trials Office, Cambridge, United Kingdom).

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