Pergamon

European Journal of Cancer Vol. 33, No. 11, pp. 1752–1758, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00135-4

Original Paper

Prophylactic Cranial Irradiation is Indicated Following Complete Response to Induction Therapy in Small Cell Lung Cancer: Results of a Multicentre Randomised Trial

A. Gregor,[1] A. Cull,[1] R.J. Stephens,[2] J.A. Kirkpatrick,[3] J.R. Yarnold,[4] D.J. Girling,[2] F.R. Macbeth,[5] R. Stout[6] and D. Machin[2]
On behalf of the United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC)

[1]Western General Hospital, Crewe Road, Edinburgh EH4 2XU; [2]Medical Research Council Cancer Trials Office, 5 Shaftesbury Road, Cambridge CB2 2BW, U.K.; [3]EORTC Data Center, Avenue E. Mounier 83, Box 11, 1200 Brussels, Belgium; [4]Royal Marsden NHS Trust, Downs Road, Sutton SM2 5PT; [5]Clinical Effectiveness Support Unit, Llandough Hospital, South Glamorgan CF64 2XX; and [6]Department of Radiotherapy, Christie Hospital, Wilmslow Road, Manchester M20 4BX, U.K.

Prophylactic cranial irradiation (PCI) reduces the risk of cranial metastasis in small cell lung cancer (SCLC), but the magnitude and value of this reduction, the risks of radiation morbidity and whether PCI influences survival are unclear. We conducted a randomised trial in patients with limited-stage SCLC who had had a complete response to induction therapy. Initially, patients were randomised equally to (1) PCI 36 Gy in 18 daily fractions, (2) PCI 24 Gy in 12 fractions and (3) no PCI; subsequently, to increase the rate of accrual, randomisation was to clinicians' choice of PCI regimen versus no PCI (at a 3:2 ratio). The endpoints were appearance of brain metastases, survival, cognitive function, and quality of life (QoL). Three hundred and fourteen patients (194 PCI, 120 No PCI) were randomised. In the revised design, the most commonly used PCI regimens were 30 Gy in 10 fractions and 8 Gy in a single dose. With PCI, there was a large and highly significant reduction in brain metastases (HR = 0.44, 95% CI 0.29–0.67), a significant advantage in brain-metastasis-free survival (HR = 0.75, 95% CI 0.58–0.96) and a non-significant overall survival advantage (HR = 0.86, 95% CI 0.66–1.12). In both groups, there was impairment of cognitive function and QoL before PCI and additional impairment at 6 months and 1 year, but no consistent difference between the two groups and thus no evidence over 1 year of major impairment attributable to PCI. PCI can safely reduce the risk of brain metastases. Further research is needed to define optimal dose and fractionation and to clarify the effect on survival. Patients with SCLC achieving a complete response to induction therapy should be offered PCI. © **1997 Elsevier Science Ltd.**

Key words: phase III trial, prophylactic cranial irradiation, small cell lung cancer, cognitive function, quality of life
Eur J Cancer, Vol. 33, No. 11, pp. 1752–1758, 1997

INTRODUCTION

AT THE time this trial was planned, in 1987, it was already clear that the cumulative risk of cranial relapse of small cell lung cancer (SCLC) rises to approximately 50% by 2 years [1–3]. Nine randomised trials, subsequently reviewed by Gregor [4], comparing prophylactic cranial irradiation (PCI) versus no PCI, suggested that PCI in modest doses significantly reduced the risk of cranial relapse. There was no evidence that PCI influenced survival; but with numbers of patients ranging from 29 to 271, none of the trials was

Correspondence to D.J. Girling.
Received 6 Sep. 1996; revised 17 Feb. 1997; accepted 11 Mar. 1997.

large enough to detect a modest but clinically worthwhile survival improvement. They also varied greatly in patient eligibility criteria, and only one assessed PCI following complete response to induction treatment, when PCI would be expected to have the greatest effect [5]. These findings, together with concerns about the possible long-term toxicity of PCI, such as ataxia, seizures and deficits in cognitive function, including dementia [6–8], led to uncertainty about the clinical usefulness of PCI.

The historical reports of serious central nervous system morbidity were in patients treated with aggressive regimens of chemotherapy and radiotherapy, often given concurrently, and receiving prolonged chemotherapy after PCI with drugs having recognised central nervous toxicity. The possibility of preventing some cerebral relapse, with its poor response to treatment and its detrimental effects on quality of life (QoL) [3, 9], together with the suggestion that late neurological damage can occur in SCLC patients without PCI and can be minimised by careful attention to the schedule and timing of PCI, led us to design the present prospective multicentre randomised trial in patients with limited stage SCLC at presentation, achieving a complete response to induction therapy. The PCI timing and schedule were chosen with great care to minimise the potential for late central nervous morbidity. The main aim was to test the effects of PCI in different dosages on cranial relapse and survival; an important secondary aim was to assess patients' cognitive function and QoL.

PATIENTS AND METHODS

Summary of initial trial design and subsequent revision

The trial opened in October 1987 with a three-way randomisation comparing (1) PCI with 36 Gy in 18 daily fractions, (2) PCI with 24 Gy in 12 daily fractions and (3) no PCI, with a planned intake of 150 patients per group (total 450). Four years later, only 100 patients had been entered from 9 centres. This poor accrual was mainly due to some radiotherapists not wishing to use the prescriptive PCI regimens. The trial was therefore redesigned and relaunched in November 1991 with the arms reduced to two: PCI versus no PCI, the choice from a recommended list of PCI regimens being left to the local radiotherapist. Centres were allowed to choose whether to study survival and cranial relapse alone or, in addition, cognitive function and QoL, using standard instruments. The randomisation ratio was changed to 3 PCI to 2 no PCI, to permit some comparison (although not randomised) between the PCI regimens; and the planned total intake was reduced to 300 patients. A further 6 centres from the U.K. and 10 from the EORTC started entering patients. The rate of intake rose from 2 to 4.5 patients per month.

Eligibility

Patients were eligible if they had had histologically confirmed SCLC of limited extent at presentation, and a complete response [10] to induction therapy, which was to have been completed no more than 8 weeks before randomisation. Local ethics committee approval and individual patient consent were required.

Treatment allocation

Patients were randomly allocated by the MRC Cancer Trials Office using a minimisation procedure, stratifying for patient's age and clinician. PCI (if allocated) had to start a minimum of 4 and a maximum of 8 weeks after completion of induction chemotherapy. It was delivered using megavoltage x-rays or cobalt gamma rays, with or without a customised shell, using opposed lateral fields with the inferior border on a line from the supra-orbital ridge to the external auditory meatus. Check films were required to ensure that the whole cranium and base of the skull were included in both fields. The dose was prescribed to the mid plane separation. PCI was not given concomitantly with chemotherapy but could be given at the same time as thoracic radiotherapy if response was already complete.

During the initial intake (1987–1991), patients were allocated to one of the following three groups.

PCI36. PCI 36 Gy in 18 daily fractions, 5 days per week.

PCI24. PCI 24 Gy in 12 daily fractions, 5 days per week.

No PCI. No PCI.

During the subsequent intake, they were allocated to one of two groups.

PCI. The choice of radiotherapy schedule was left to the local radiotherapist but the total dose was not to exceed 40 Gy in 2 Gy fractions. The following schedules, given in equal fractions daily except at weekends, were recommended: 20 Gy in 5 fractions, 24 Gy in 8 fractions, 30 Gy in 10 fractions and 36 Gy in 18 fractions.

No PCI. No PCI.

Assessments and reports

Patients were assessed at randomisation, at 6 and 12 months from randomisation, and then annually until death. The information collected included details of previous treatment and investigations (including brain CT scan), details of PCI schedule, evidence of brain metastases and date and cause of death.

Assessment of cognitive function and QoL

The redesigned trial included formal psychometric evaluation which centres were instructed to perform blind with respect to PCI status. The National Adult Reading Test (NART) [11, 12] was administered at randomisation, to provide an estimate of intellectual ability. The Paced Auditory Serial Addition Task (PASAT) [13], the Rey Osterrieth Complex Figure Test (CFT) [14] and the Auditory Verbal Learning Test (AVLT) [15] were administered at each assessment. Impairment was defined: (a) in the PASAT as fewer than 21 correct answers in adding pairs of consecutive numbers in a total of 60 integers between 1 and 9 read at a fixed speed; (b) in the CFT as a memory score of less than half the copy score; (c) in the AVLT learning component as a failure to recall 5 or more new items during five readings of a list of 15 objects; and (d) in the AVLT retention component as forgetting 4 or more items from the original list after a separate unrelated list had been read out. Thus, assessments were made of auditory mental tracking (PASAT), perceptual organisation and visual memory (CFT) and memory span and verbal learning (AVLT). QoL (physical and psychological symptoms and activities of daily living) and anxiety and depression were assessed at each assessment using the Rotterdam Symptom Checklist (RSCL) [16] and the Hospital Anxiety and Depression Scale (HADS) [17].

Statistical methods

The planned intake of 300 patients was chosen to enable an increase in the 2-year survival rate from 5% to 15% to be detected with 5% significance and 90% power. The Kaplan–Meier estimate was used to calculate brain metastasis rates, patients without metastases being censored at the time they were last seen alive or at date of death. Survival was calculated from the date of randomisation until death, survivors being censored at the date they were last known to be alive. The Kaplan–Meier estimate was used to calculate survival curves and the Mantel–Cox version of the log-rank test to make treatment comparisons. Associated confidence intervals (CIs) were calculated for the corresponding hazard ratios (HRs). The trial data were managed using the COMPACT program [18].

RESULTS

Patients in the trial

Between October 1987 and April 1995, 314 patients were randomised from 18 centres in the U.K. and 10 in continental Europe: 194 to PCI and 120 to No PCI. The characteristics of the patients at randomisation are shown in Table 1. A variety of chemotherapy regimens was used; the commonest, in order of frequency, were doxorubicin, cyclophosphamide and etoposide (ACE); ifosfamide, cisplatin and etoposide (ICE); carboplatin and etoposide; ACE plus methotrexate; ACE plus vincristine, and ICE plus vincristine.

PCI received

A variety of PCI regimens was used (Table 2). In the initial intake, 32 patients were randomised to PCI36 and 32 to PCI24. In the subsequent intake, the most frequent regimen was 30 Gy in 10 fractions (61 patients), followed by 8 Gy in a single dose (25 patients).

Appearance of brain metastases

Kaplan–Meier estimates of the percentages of patients with brain metastases are shown in Figure 1. There was a large and highly significant difference in favour of the PCI group (HR = 0.44, 95% CI 0.29–0.67, $P = 0.00004$). The percentages were 30% in the PCI group and 54% in the No PCI group at 2 years and 38% and 54% at 3 years. The initial randomised three-arm comparison (Figure 2) showed little if any difference between the PCI24 and the No PCI groups (HR = 0.71, 95% CI 0.36–1.43), but a highly significant difference between the PCI36 and the No PCI groups (HR = 0.16, 95% CI 0.07–0.36, $P = 0.0007$).

Table 1. Characteristics of the 314 patients at randomisation

Characteristic	PCI ($n = 194$)	No PCI ($n = 120$)	Total ($n = 314$)
Sex			
Male	125 (64%)	74 (62%)	199 (63%)
Female	69 (36%)	46 (38%)	115 (37%)
Age (years)			
Median	60	61	60
Range	37–79	28–76	28–79
Thoracic radiotherapy given	164 (85%)	99 (83%)	263 (84%)
CT brain scan performed	33 (17%)	16 (13%)	49 (16%)

Table 2. PCI received

PCI received Gy/fractions	Patients
Randomised to 36/18	32
36/18	27
24/12	1
40/15	1
none	3
Randomised to 24/12	32
24/12	31
24/10	1
PCI regimen chosen by clinician	130
8/1	25
20/5	7
24/8	1
24/12	2
25/10	2
26/13	1
30/8	1
30/10	61
30/12	9
30/15	13
30/20	1
36/18	2
none	5

Survival from randomisation

Of the 314 patients, 231 have died and the remaining 83 have been followed up for a median of 18 months. The survival comparison by treatment group is shown in Figure 3. The advantage to PCI is not statistically significant (HR = 0.86, 95% CI 0.66–1.12, $P = 0.25$). Median survival was 305 days in the PCI group and 300 in the No PCI group; the estimated survival rates were 44% and 39% at 1 year, 25% and 19% at 2 years and 21% and 11% at 3 years, respectively.

Brain-metastasis-free survival

There was a statistically significant advantage to PCI in brain-metastasis-free survival (HR = 0.75, 95% CI 0.58–0.96, $P = 0.02$).

Results of cognitive function and QoL tests

In all, 136 patients (84 PCI, 52 No PCI) were included in the optional assessments of cognitive function and QoL. Data were received for 125 (92%) at baseline, 59 (56%) of 106 assessable at 6 months, 32 (63%) of 54 at 1 year and 9 (45%) of 20 at 2 years. 7 patients still alive have yet to reach the time for assessment at 1 year, and 21 at 2 years.

Cognitive function assessments were made at baseline on 76 PCI and 49 No PCI patients. Of these, 18 (24%) PCI and 12 (24%) No PCI had impairment on PASAT, 32 (42%) and 20 (41%) on CFT, 29 (38%) and 15 (31%) on AVLT learning and 18 (24%) and 13 (27%) on AVLT retention. Thus, the proportions of patients showing impairment in each test were substantial but similar in the two groups.

For each test, patients without impairment at baseline who became impaired are shown in Table 3. All the tests

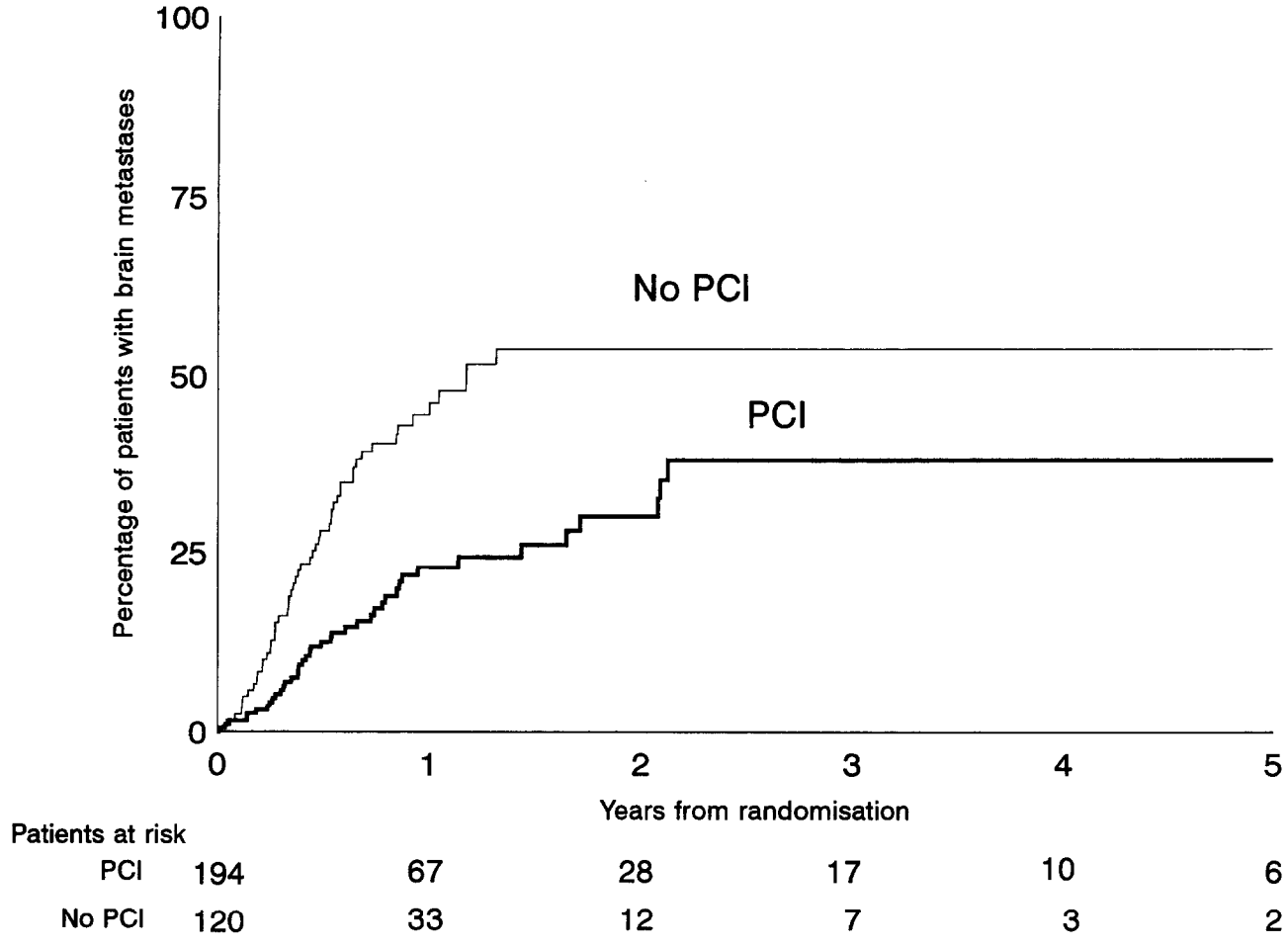

Figure 1. Percentage of patients with brain metastases from the date of randomisation.

showed some evidence of new impairment at 6 months and at one year, but there was no evidence of sustained deterioration with time and no notable difference between the PCI and No PCI groups and thus, no evidence of major impairment attributable to PCI at these relatively early time points.

On the RSCL assessments, the most common symptoms reported by patients at baseline were, in order of decreasing frequency, tiredness, loss of hair, lack of energy, anxious feelings, worrying, shortness of breath, irritability and cough. Loss of hair was moderate or severe in almost all the patients with this symptom, and tiredness and lack of energy in approximately half, but the other symptoms were mild in the vast majority of patients. The symptoms showing greatest deterioration from baseline to 6 months are shown in Table 4. For all of the six commonest symptoms, deterioration was worse in the No PCI than in the PCI group.

On the RSCL, the vast majority (93%) of patients reported normal or near normal (grade 0 or 1) activities of daily living at baseline, 6 months and 1 year. On the HADS, 13 (23%) of the 56 patients assessed had borderline anxiety and 5 (9%) clinically significant anxiety at 6 months and 4 (13% of 31) and 4 (13%), respectively at 1 year. The corresponding figures for depression were 6 (11%) borderline and 4 (7%) clinically significant at 6 months and 2 (6%) and 1 (3%) at 1 year. There were no differences between the PCI and No PCI groups.

DISCUSSION

This trial has confirmed that PCI, given at the end of induction therapy, substantially reduced the likelihood of cranial relapse of small cell lung cancer. This finding supports the previously reported trials [4, 19, 20]. The estimated risk was reduced from 54% to 30% at 2 years after randomisation and from 54% to 38% at 3 years, a substantial gain in a situation with devastating consequences for patients. There was also a statistically significant improvement in brain-metastasis-free survival in the PCI group. Nevertheless, PCI fails to eliminate the risk of brain metastases completely and ongoing follow-up is necessary to establish the ultimate rates.

The first part of the present trial included a randomised comparison of the two PCI dosages, 36 Gy and 24 Gy given in 2 Gy fractions. The higher dose was more effective in reducing the risk of brain metastasis. This demonstration of dose response for PCI is the first such evidence and is important in view of previous recommendations for low PCI dose as a means of reducing toxicity [20]. The trial reported by Arriagada and his colleagues using a 24 Gy schedule had a cranial relapse rate of 40% at 2 years [20]. This schedule

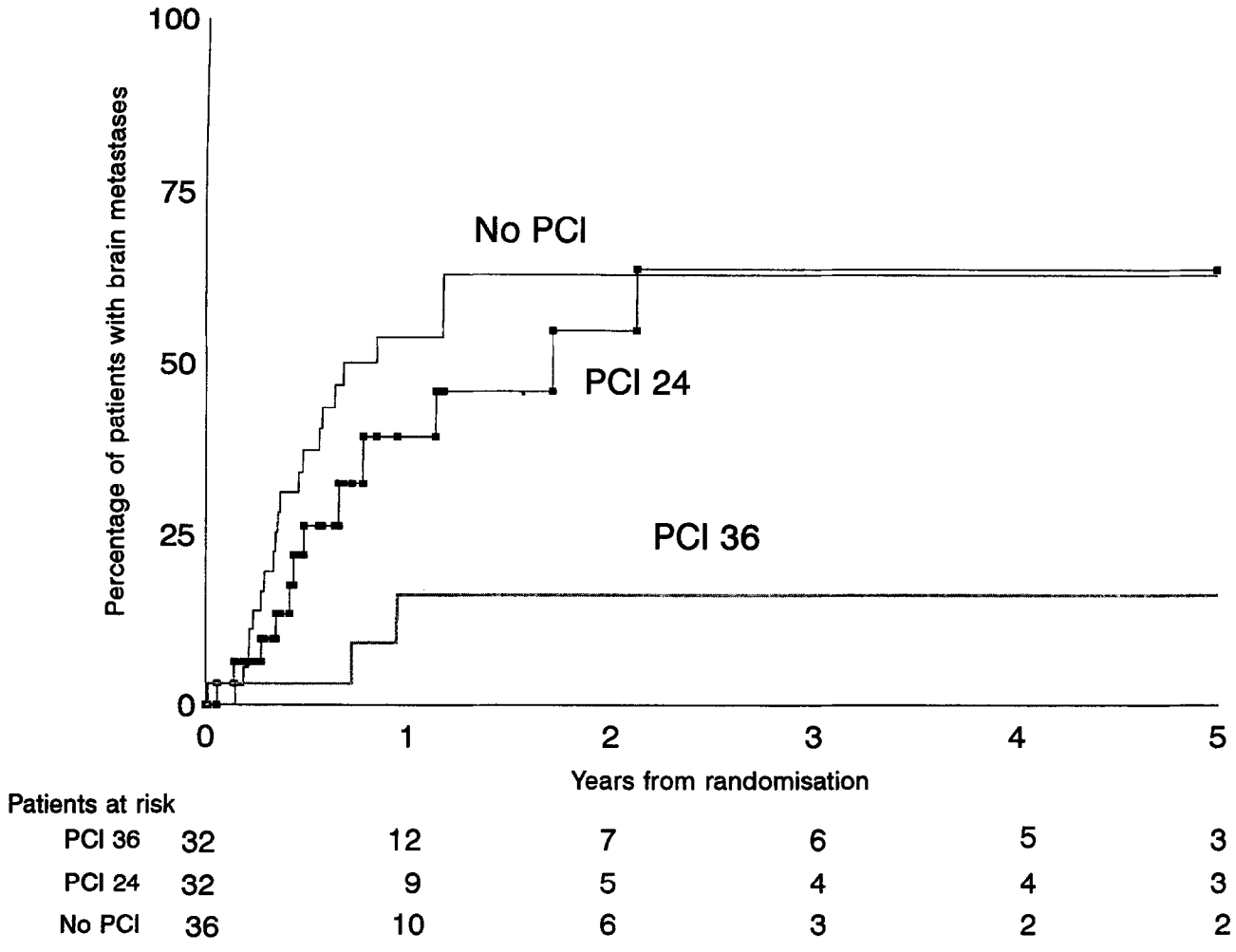

Figure 2. Percentage of patients with brain metastases from the date of randomisation in the initial three-arm comparison.

was delivered in 8 fractions rather than the 12 that we used, achieving a higher biological dose. Further trials are therefore needed to determine if increased doses of PCI can reduce brain metastasis further without increasing the risk of long-term neurological toxicity.

There was a suggestion of improved survival in the PCI group, but the difference was not statistically significant. No individual randomised trial has conclusively shown a survival benefit for PCI. However, none of these trials was large enough to provide sufficient power to detect small differences. It has been suggested that patients have the best prospect of long-term survival and new metastases are less likely to occur if any residual disease is minimal at the time PCI is given [20, 21]. Because individual trials will have small numbers of long-term survivors, this question is now being addressed by a meta-analysis conducted jointly by the Institut Gustave Roussy and the Meta-analysis Group of the MRC Cancer Trials Office, using updated individual patient data [22]. If a survival advantage is confirmed, it will be interesting to determine whether it is most evident in complete responders. To date, we have identified only seven relevant randomised trials restricted to complete responders, and of these, only four, including the present trial, have been published [19, 20, 23].

The present trial differs from all the others in its prospective neuropsychometric assessment of toxicity. In the revised version of the protocol, centres were given the option of comparing not only survival and cranial relapse rates but also cognitive function and QoL using standard instruments. Participation in this part of the trial was a major undertaking; assessors in each centre had to be trained to apply the tests reliably and each assessment took approximately 40 min to complete. Unsurprisingly, not all centres were able to collaborate in this aspect of the trial and, in those centres that did participate, the levels of compliance in providing the data, although high at baseline, were less so subsequently.

Much concern has been expressed, mainly in the United States, about the possible long-term damaging effects that PCI can have on the central nervous system. These include ataxia, seizures and dementia [6–8, 23–27]. However, much of this evidence has come from non-randomised comparisons, retrospective surveys or recall assessments limited to small numbers of long-term survivors. There is evidence that the risks are highest when chemotherapy (especially with neurotoxic drugs such as nitrosoureas) is given simultaneously with PCI (especially with large fraction sizes) [7]. In contrast, a review of 65 European long-term survivors

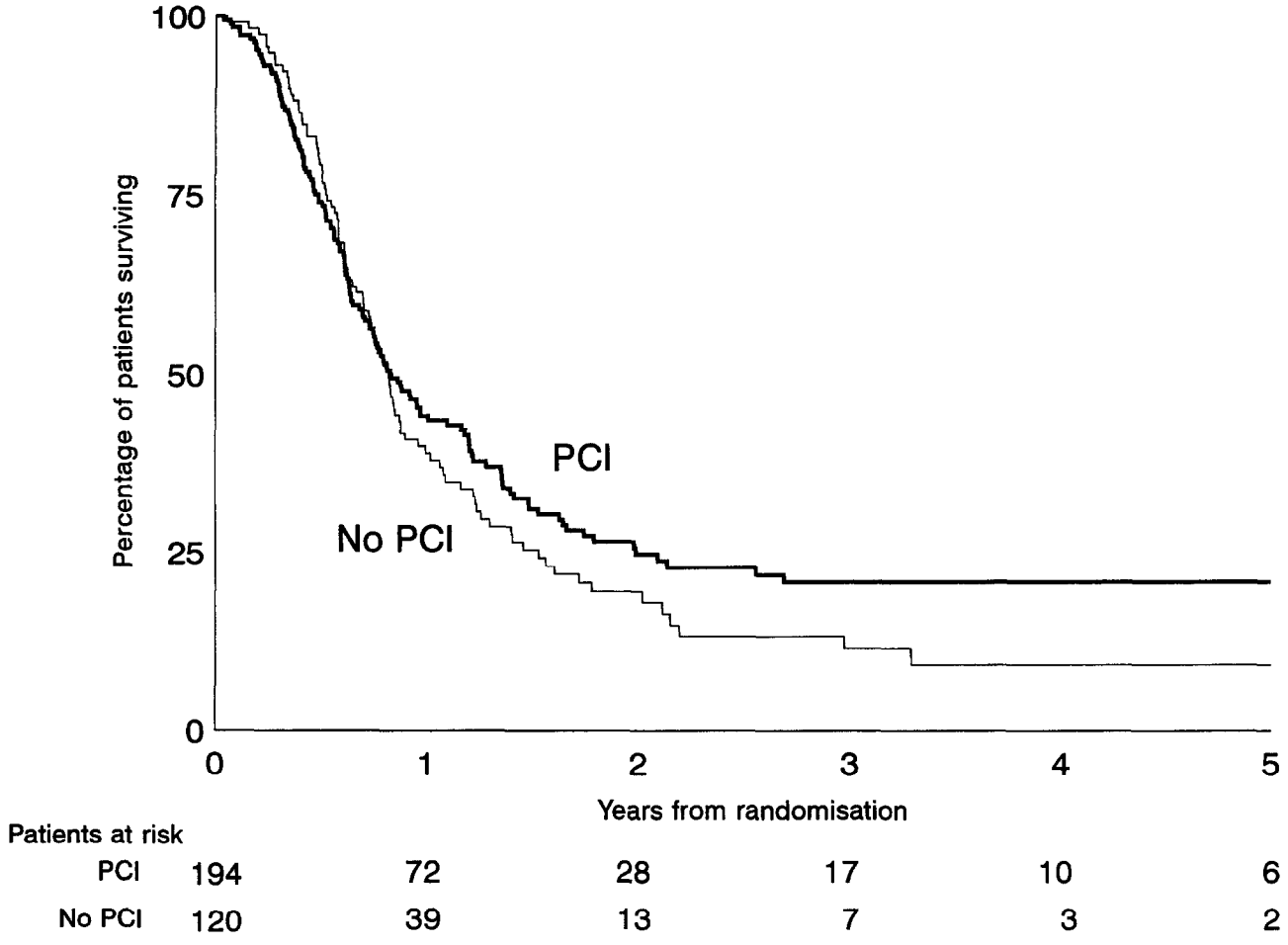

Figure 3. Percentage of patients surviving from the date of randomisation.

suggested that in patients given PCI after completion of chemotherapy, the impact of neuropsychometric deficits on QoL is minor [28]. Our findings, based on thorough, systematic and prospective assessments of cognitive function, are therefore of considerable interest. An important observation was that, even in this group of complete responders to induction therapy, who are likely to be among the fittest of patients with SCLC, there were substantial levels of impairment at randomisation, before PCI had been given. With the PCI regimens studied, given after induction therapy had been completed, there was additional impairment at 6 months and 1 year, but no evidence of any consistent difference between patients given or not given PCI and thus no evidence of any major impairment attributable to PCI. Deterioration in general symptoms was reported by patients more frequently in the No PCI than in the PCI group, a finding that we hope other research workers will address.

In conclusion, we would recommend that PCI be offered to all patients with limited SCLC in complete response to their induction treatment. By this means, the devastating effects of brain metastases and the costs of treating them, will be avoided in a substantial proportion of patients, without clinically significant risks of central nervous system radi-

Table 3. Occurrence of cognitive function impairment in patients without impairment at baseline

	Impairment at			
	6 months		1 year	
Cognitive function test	PCI (%)	No PCI (%)	PCI (%)	No PCI (%)
PASAT	5/26 (19)	3/21 (14)	5/16 (31)	2/12 (17)
CFT	4/18 (22)	1/19 (5)	2/13 (15)	2/12 (17)
AVLT learning	7/23 (30)	5/17 (29)	9/13 (69)	4/10 (40)
AVLT retention	4/26 (15)	3/17 (18)	0/16 (0)	3/8 (38)

Table 4. Symptoms reported absent or mild at baseline that were moderate or severe at 6 months

Symptom	PCI (%)	No PCI (%)
Tiredness	4/17 (24)	4/7 (57)
Lack of energy	3/17 (18)	4/11 (36)
Irritability	3/21 (14)	5/14 (36)
Decreased sexual interest	2/11 (18)	3/11 (27)
Shortness of breath	4/21 (19)	3/11 (27)
Cough	3/20 (15)	3/13 (23)

ation damage. PCI is simple and cheap to give. It can be given concurrently with thoracic radiotherapy, which, following a recent meta-analysis, is recommended for all patients with limited SCLC [29]. We are currently planning a new randomised trial comparing different PCI dosage schedules.

1. Bunn PA, Nugent JL, Matthews MJ. Central nervous system metastases in small-cell bronchogenic carcinoma. *Semin Oncol* 1978, **5**, 314–322.
2. Komaki R, Cox JD, Whitson W. Risk of brain metastases from small-cell carcinoma of the lung related to the length of survival and prophylactic irradiation. *Cancer Treat Rep* 1981, **65**, 811–814.
3. Lucas CF, Robinson B, Hoskin PJ *et al.* Morbidity of cranial relapse in small-cell lung cancer and the impact of radiation therapy. *Cancer Treat Rep* 1986, **70**, 565–570.
4. Gregor A. Cranial irradiation in small cell lung cancer. *Br J Cancer* 1991, **63**, 13–14.
5. Aroney RS, Aisner J, Wesley MN, *et al.* Value of prophylactic cranial irradiation given at complete remission in small cell lung carcinoma. *Cancer Treat Rep* 1983, **67**, 675–682.
6. Catane R, Schwade JG, Yarr I, *et al.* Follow-up neurological evaluation in patients with small cell lung carcinoma treated with prophylactic cranial irradiation and chemotherapy. *Int J Radiat Oncol Biol Phys* 1981, 7, 105–109.
7. Johnson BE, Becker B, Goff WB, *et al.* Neurologic, neuropsychologic and computed cranial tomography scan abnormalities in 2 to 10-year survivors of small cell lung cancer. *J Clin Oncol* 1985, **3**, 1659–1667.
8. Johnson JR, Morgan DAL, Holland IM. Prophylactic cranial irradiation for small cell lung cancer: long-term results. *Clin Oncol* 1989, **1**, 24–27.
9. Felletti R, Souhami RL, Spiro SG, *et al.* Social consequences of brain or liver relapse in small cell carcinoma of the bronchus. *Radiother Oncol* 1985, **4**, 335–339.
10. World Health Organization. *WHO Handbook for Reporting Results of Cancer Treatment.* WHO Offset Publication No. 48, Geneva, WHO, 1979.
11. Nelson HE. *National Adult Reading Test.* Windsor, NFER-Nelson, 1982.
12. Ebmeier KP, Booker K, Cull A, Gregor A, Goodwin GM, O'Carroll RE. The validity of the National Adult Reading Test in estimating premorbid intellectual ability in long-term survivors of hemispheric glioma and whole brain irradiation. *Psycho-Oncol* 1993, **2**, 133–137.
13. Gronwall DMA. Paced Auditory Serial Addition Task: a measure of recovery from concussion. *Percept Motor Skills* 1977, **44**, 367–373.
14. Osterrieth PA. Le test d'une copie d'une figure complexe. *Arch Psychol* 1944, **30**, 206–356.
15. Rey A. *L'examen Clinique en Psychologie.* Paris, Presses Universitaire de France, 1964.
16. de Haes JCJ, Knippenberg FCE, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990, **62**, 1034–1038.
17. Zigmond AS, Snaith RR. The Hospital Anxiety and Depression Scale. *Acta Psychiat Scand* 1983, **67**, 361–370.
18. COMPACT Steering Committee. Improving the quality of clinical trials in cancer. *Br J Cancer* 1991, **63**, 412–415.
19. Ohonoshi T, Ueko H, Kawahara S, *et al.* Comparative study of prophylactic cranial irradiation in patients with small cell lung cancer achieving a complete response: a long-term follow-up result. *Lung Cancer* 1993, **10**, 47–54.
20. Arriagada R, Le Chevalier T, Borie F, *et al.* Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst* 1995, **87**, 183–190.
21. Rosen ST, Makuch RW, Lichter AS, *et al.* Role of prophylactic cranial irradiation in prevention of central nervous system metastases in small cell lung cancer: potential benefit restricted to patients with complete response. *Am J Med* 1983, **74**, 615–624.
22. Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993, **341**, 418–422.
23. Laukkanen E, Klonoff H, Allan B, Graeb D, Murray N. The role of prophylactic brain irradiation in limited stage small cell lung cancer: clinical neuropsychologic and CT sequelae. *Int J Radiat Oncol Biol Phys* 1988, **14**, 1109–1117.
24. Fleck JF, Einhorn LH, Lauer RC, Schultz SM, Miller ME. Is prophylactic irradiation indicated in small-cell lung cancer? *J Clin Oncol* 1990, **8**, 209–214.
25. Turrisi AT. Brain irradiation and systemic chemotherapy for small-cell lung cancer: dangerous liaisons? *J Clin Oncol* 1990, **8**, 196–199.
26. Crossen JR, Garwood D, Glatstein E, Neuwelt EA. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. *J Clin Oncol* 1994, **12**, 627–642.
27. Shaw EG, Su JQ, Eagan RT *et al.* Prophylactic cranial irradiation in complete responders with small-cell lung cancer: analysis of the Mayo Clinic and North Central Cancer Treatment Group data bases. *J Clin Oncol* 1994, **12**, 2327–2332.
28. Cull A, Gregor A, Hopwood P, *et al.* Neurological and cognitive impairment in long-term survivors of small cell lung cancer. *Eur J Cancer* 1994, **30A**, 1067–1074.
29. Pignon J-P, Arriagada R, Ihde DC, *et al.* A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *New Engl J Med* 1992, **327**, 1618–1624.

Acknowledgements—The following consultants entered patients into the trial and are co-authors. Antwerp, Belgium: D. Galdemans, J. van Meerbeeck; Clatterbridge, U.K.: P.I. Clark, B. Cottier, J. Littler; Dublin, Ireland: L. Clancy; Dundee, U.K.: S.N. Das; Edinburgh, U.K.: M.A. Cornbleet, V. Cowie, A. Gregor, J.F. Smyth; Gdansk, Poland: H. Karnicka; Genoa, Italy: A. Ardizzoni; Glasgow, U.K.: P. Canney, T.B. Habeshaw, A.N. Harnett, E.J. Junor, F.R. Macbeth, W. Martin, J.M. Russell, H.M.A. Yosef; Groningen, The Netherlands: H.J.M. Groen; London, U.K.: F. Calman, G.M. Duchesne, P.G. Harper, R.M. Rudd, R.L. Souhami, M.I. Spittle, J.S. Tobias; Manchester, U.K.: P.A. Burt, R. Stout, N. Thatcher; Naples, Italy: C. Gridelli; Newcastle Upon Tyne, U.K.: J.M. Bozzino, Oxford, U.K.: N.P. Rowell; Perugia, Italy: L. Crino; Prague, Czech Republic: J. Dolenský; Rotterdam, The Netherlands: P.A. Helle, M.J.M. van Mierlo, P.J.C.M. Nowak, M.J.J. Olofsen-van Acht, S. Senan; Sheffield, U.K.: J.J. Bolger; Southend, U.K.: A.D. Davidson, A. Lamont, C.W. Trask; Sutton, U.K.: M. Brada, H.T. Ford, I.E. Smith, J.R. Yarnold; Tilburg, The Netherlands: B. Maat, S.B. Oei, Ph. Poortmans, P. Rodrigus; Torino, Italy: M. Clerico, G. Scagliotti; Wolverhampton, U.K.: D.J. Fairlamb. Local coordinators were: C. Ball, N. Gower, J. Hodgetts, S. Hons, P. Hoynck, J. Hutchinson, L. James, J. A. Kirkpatrick, L. Lomax, S. Lynch, K. McGregor, K. Priest, M. Stewart, V. Turnbull, M. van der Hulst and A. Young.