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Clinical Study

Efficacy and safety of prophylactic cranial irradiation in patients with small cell lung cancer

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Summary

Background: Prophylactic cranial irradiation (PCI) as part of the treament regimen for patients with limited stage small cell lung cancer (SCLC) remains controversial. The present study was performed to analyze the efficacy and safety of PCI in patients with limited stage SCLC who achieved complete remission.

Patients and methods: Between 1983 and 1993, thirty-nine patients with limited stage SCLC who had shown complete remission after chemotherapy were enrolled prospectively into the non-randomized study. Eighteen of them received PCI (PCI^+), while 21 did not (PCI^-). Pretreatment CT or MRI of the brain was performed in all patients. Patients were prospectively evaluated by a neurologist at regular intervals. *Results:* Three PCI^+ patients and seven PCI^- patients developed brain metastases. The frequencies of brain metastases were not significantly different between the groups (Fisher's exact test, $p = 0.207$), but brain metastases in PCI^+ patients tended to occur later (log rank, $p = 0.008$). Overall survival was significantly longer in PCI^+ patients (log rank, $p < 0.001$).

Early toxicity consisted of headache, nausea, fatigue, concentration problems and alopecia. These symptoms and signs were mild and usually reversible within a few months. Late toxicity was studied in patients whose survival exceeded two years. Seven PCI^+ patients survived for more than two years, while no PCI^- patients survived for more than two years. Memory problems were seen in six of the seven patients. These problems were non-disabling and, once established, remained stable for months to years.

The most prominent radiologic abnormalities were cortical atrophy and leukoencephalopathy, found in four of the five patients who underwent radiologic follow-up examination.

Conclusions: This non-randomized study suggests that PCI may be effective by decreasing the frequency of brain metastases and by increasing the brain metastasis-free survival and overall survival, with a minor risk of clinical and radiologic neurotoxicity.

Introduction

Small cell lung cancer (SCLC), which accounts for approximately one quarter of the cases of lung cancer, is characterized by highly aggressive behavior, resulting in early metastasis [1]. Combination chemotherapy is the cornerstone of treatment for this disease, resulting in a slightly better prognosis in terms of survival [2]. The occurrence of brain metastases is the most frequent neurologic complication in SCLC, and is associated with high morbidity and mortality [3, 4]. The risk of cerebral metastases is proportional to the length of survival, with a two-year probability of 80 percent [5].

One of the hypotheses to explain the increased occurrence of brain metastases with prolonged sur-

vival describes the central nervous system (CNS) as a sanctuary site for residual tumor cells, where metastases can grow beyond the reach of chemotherapy as a result of the blood-brain barrier [6]. It may be possible to eradicate these tumor cells by radiotherapy.

Prophylactic cranial irradiation (PCI) has been introduced to reduce CNS metastases. In the 1970s, several randomized studies were performed to evaluate the efficacy of PCI. PCI seemed to be effective in decreasing the central nervous system relapse rate in patients with limited stage small cell lung cancer (confined to one hemithorax) who showed complete remission, although overall survival was not found to be consistently improved [7, 8]. PCI failure with regard to survival is partially explained by the fact that CNS relapse is associated with the recurrence of thoracic disease. In only 5 percent of the patients was CNS was the sole site of relapse. Another possible explanation is that none of the studies were large enough to detect small differences in survival. Moreover, the role of PCI became a controversial topic, as PCI potentially contributed to late neurotoxicity in patients with SCLC [9–13].

The present paper shows the results of a prospective neurologic follow-up study in a cohort of 243 consecutive patients with small cell lung cancer, and was performed to assess the efficacy and safety of PCI in this population. The patients were diagnosed and treated in one institution. Only patients with limited stage small cell lung cancer were given PCI. The treatment regimen was generally uniform, except for the use of PCI.

Patients and methods

Patients

Between January 1983 and December 1993, 248 patients with newly diagnosed SCLC were included in the study. The diagnosis of SCLC was proved by histologic or cytologic examination. To detect areas of distant metastases, initial staging by the pulmonologist consisted of physical examination, routine blood and chemistry profile, chest X-ray, chest computerized tomography (CT), fiber optic bronchoscopy, ultrasound and CT of the abdomen, CT of the brain, radionuclide bone scan, and bone marrow aspirates. After the end of 1990, CT of the brain was replaced by magnetic resonance (MR) imaging and MR bone scans were routinely performed.

Limited disease (LD) was defined as the tumor being confined to one hemithorax, with or without ipsilateral mediastinal or supraclavicular lymph node involvement. Patients with tumor which had spread beyond these sites were classified as having extensive disease (ED). Eighty-one consecutive patients (33%) with limited disease were the subjects of this prospective study on the efficacy and safety of prophylactic cranial irradiation.

Treatment and clinical assessment

All patients were treated according to standard protocols, with a combination chemotherapy regimen consisting of cyclophosphamide, doxorubicin and etoposide, this cycle being repeated at 3–4 week intervals to a maximum of five courses.

Restaging was performed after five courses of chemotherapy and consisted of clinical, radiologic and fiberoptic endoscopic examinations. Complete remission (CR) was defined as total clinical, radiologic and pathologic resolution of the disease.

PCI was administered only to patients with limited disease who showed CR, and was given approximately three weeks after the entire chemotherapy had been completed. Patients were treated with a parallel pair technique, using a linear accelerator (6 MV photons). The dose was calculated in the midline. Total PCI dose was 3000 cGy, delivered in 10 fractions over a period of 2.5 weeks. After 1988, the fraction dose was reduced to 200 cGy and delivered in 15 fractions over three weeks. As of 1990, PCI was excluded from the treatment regimen.

Following completion of treatment, patients were evaluated every six weeks at the pulmonary outpatient clinic, using a physical examination, chest radiograph and hematologic and biochemical tests. During initial staging, all patients were routinely referred to the Department of Neurology for

an assessment of possible CNS involvement. All patients underwent a neurologic examination by an experienced neuro-oncologist. Patients were prospectively evaluated by the same neuro-oncologist every three months for the first year, and biannually after that. Follow-up CT and MR were performed on indication only. The patients were followed until death or for at least two years.

In patients with long-term survival (at least two years from initial diagnosis), an additional CT or MR was performed. Neurologic and radiologic abnormalities were designated as treatment-related unless clearly explainable otherwise.

Images obtained with CT or MR were reviewed by an experienced neuroradiologist (JTW). Images were evaluated for cortical atrophy, extent of white matter lesions, ventricular enlargement and comparison of cerebral and cerebellar atrophy. Cortical atrophy was rated as absent if no sulcus was wider than 5 mm (I), as slight if a few sulci were wider than this value (II), as moderate if more sulci but fewer than half were wider than 5 mm (III), and as severe if more than half of the sulci were wider than 5 mm (IV). The extent of white matter lesions was scored as none if no such lesions were present (I), as slight if white matter lesions were restricted to a periventricular zone with a width of no more than one ventricle (II), as moderate if white matter lesions were scattered throughout the corona radiata excluding the internal capsule, and as severe if the entire hemispheric white matter was affected. Ventricular enlargement was rated using to the Evans index [14]. Visual assessment was used for the comparison of cerebral and cerebellar sulci. (I – cerebral sulci less prominent than cerebellar, II – cerebral sulci equal to cerebellar, III – cerebral sulci more prominent than cerebellar).

Statistical analysis

Fisher's exact test was used to compare the frequencies of CNS metastases in patients treated with and without PCI.

Survival curves were drawn using the Kaplan-Meier product-limit method. The log-rank test was applied to evaluate the differences between the survival curves. The rather small groups did not justify multivariate analyses incorporating more variables.

A p-value below 0.05 was considered statistically significant.

Results

Thirty-nine SCLC patients (29 males and 10 females) had limited disease and complete resolution of the disease at restaging. The median age at the time of initial diagnosis was 63 years (range 31–84). PCI was administered to 18 patients (46%) after five chemotherapy courses (PCI^+). Between 1983 and 1990, two eligible patients refused PCI. Because PCI was excluded from the treatment protocol after 1990, the other 19 patients did not receive PCI (PCI^-). Patients with and without PCI did not differ significantly in sex and age.

Fifteen patients received PCI (79%) at a dose of 30 Gy in 10 fractions. The others received PCI at a dose of 30 Gy in 15 fractions.

Relapse and survival analysis

Thirty-four of the entire group of 39 patients (87%) relapsed. Recurrence at the site of the primary tumor was most common (85%). Initial brain relapse occurred in five patients (15%).

Three PCI^+ patients (17%) developed brain metastases, this being in all three the first site of clinically manifested relapse. In two of them intrathoracic recurrence was diagnosed within one month, while the other showed no signs of tumor activity outside the CNS. Median time from the initial diagnosis of SCLC to the detection of brain metastases was 16 months, with a range of 12 to 22 months. Median overall survival (time between initial diagnosis and death) in all patients receiving PCI was 18 months (range 7–144). One patient is still alive at the time of writing. Survival after detection of brain metastases ranged from one day to eight weeks.

Brain relapses occurred in seven of the 21 PCI^- patients (33%). Median brain metastasis-free survival (time between initial staging and detection of

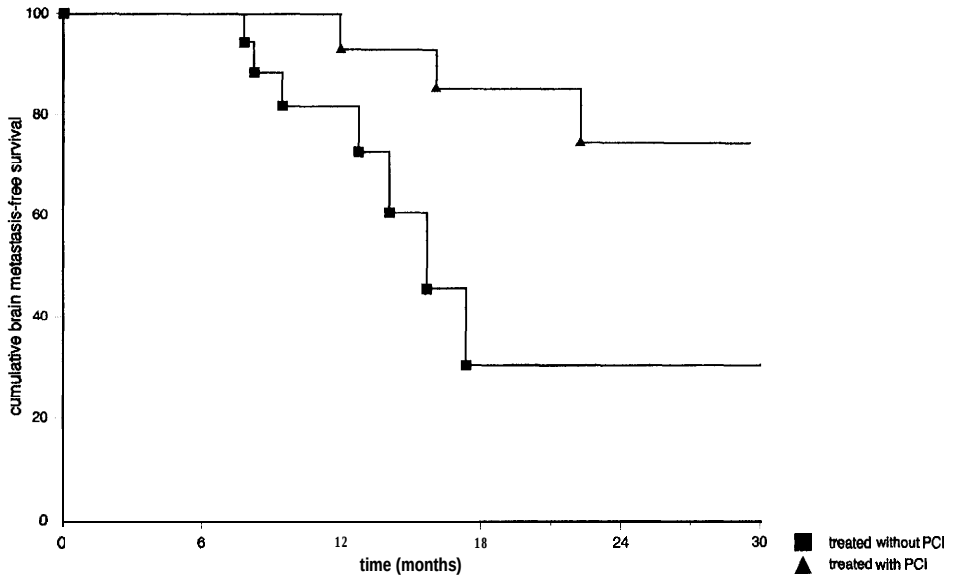


Figure 1. Survival curves of brain metastasis-free survival in 39 patients with limited stage small cell lung cancer and complete remission after chemotherapy. The difference between the curves is not statistically significant (logrank 6.95, p = 0.008).

brain metastases) was 13 months (range 8-17). The brain was the first site of relapse in two patients. Tumor activity outside the CNS was confirmed within one month in both. Median survival from diagnosis of brain metastases was O-7 months. Patients treated without PCI had a median overall survival of 13 months (range 7-19). None of them are still alive.

The occurrence of brain metastases was not significantly different in patients with or without PCI (Fisher's exact test, p = 0.207).

Figure 1 shows the curves of brain metastasis-free survival in patients with and without PCI. The difference between the curves, using the log-rank test, was significant (log-rank 6.95, p = 0.008).

Overall survival curves for all patients with limited stage SCLC who showed CR are presented in Figure 2. The log-rank test indicated a statistically significant difference between the curves in favor of PCI' patients (log-rank 11.65, p < 0.001).

Early neurologic toxicity

Early neurologic sequelae were assessed in 17 patients receiving PCI. Early toxicity developed during the administration of PCI and within a period of three months after termination. Six of the 17 patients experienced headache and nausea during the radiotherapy administration. One of them needed a brief course of corticosteroids, resulting in relief. In the others, headache was relatively mild.

Five patients experienced a short period of increased fatigue and increased need of sleep. Five patients experienced concentration and memory problems within two months. which proved reversible in two.

All patients experienced alopecia. which proved reversible within four months in all.

Late neurologic toxicity

Late neurologic toxicity was assessed in seven patients with limited disease, complete remission and survival times of more than two years. All of them were treated with PCI.

Memory problems surfaced as the most frequent possibly treatment-related complication in six patients. Immediate recall was usually affected. The memory decline was insidious and started within six months after termination of therapy in four patients and after a year in the others. Once established, the

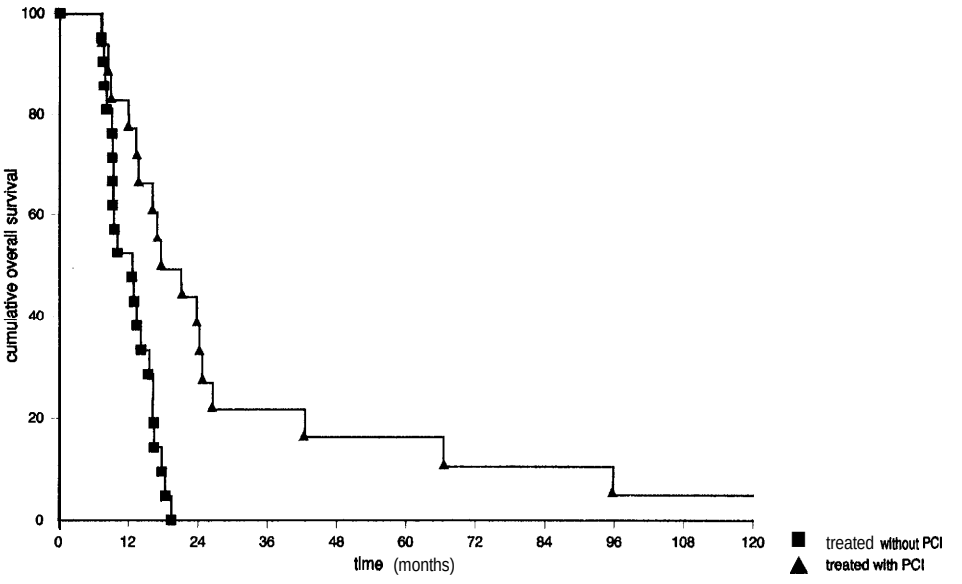


Figure 2. Survival curves of overall survival in 39 patients with limited stage small cell lung cancer and complete remission after chemotherapy. The difference between the curves is highly statistically significant in favor of patients treated with PCI (logrank 11.65, $p < 0.001$).

memory problems remained stable for months to years in most patients. These problems were non-disabling, and could in all cases be documented by neuropsychological assessment.

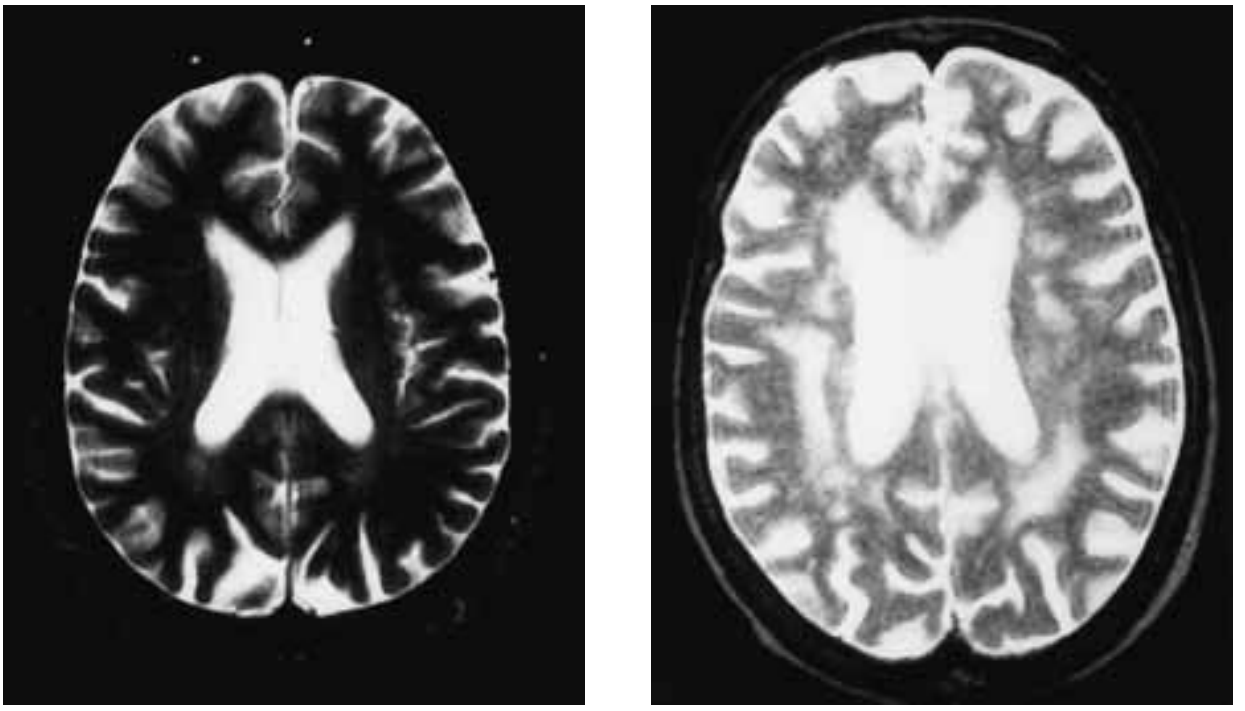
In six of the seven patients surviving for more than two years, a follow-up radiologic examination of the brain was performed. One CT was not available for reexamination. MR imaging was performed in three patients, CT in the others. Clinically, these five patients had memory problems. One patient had no signs of cortical atrophy. Mild cortical atrophy was present in one patient. Moderate atrophy was found in two patients and severe atrophy in one.

Periventricular and subcortical leukoencephalopathy was absent in one patient, and present in four, classified as grade II in one and as grade III in three patients. Figure 3a and b demonstrate differences in grade of atrophy and extent of white matter lesions.

The Evans index was abnormal in one patient and normal in four. Supratentorial cortical sulci were less prominent than infratentorial sulci in four of the patients. In one patient, the supratentorial atrophy was in proportion with infratentorial atrophy. Radiologic abnormalities are shown in Table 1.

Table *1.* Radiologic abnormalities in five PCI⁻ patients surviving for more than two years

	Neurologic abnormalities present (N = 5)
Cortical atrophy	
Grade I	1
Grade II	1
Grade III	2
Grade IV	1
Leukoencephalopathy	
Grade I	1
Grade II	1
Grade III	3
Grade IV	–
Evans index	
Normal	4
Abnormal	1
Tentorium ratio	
Grade I	4
Grade II	1
Gradc III	



A B

Figure 3. A. MRI of the brain in a 55-year old man three years after diagnosis of SCLC. T_2-weighted image shows no cortical atrophy and the absence of periventricular and subcortical leukoencephalopathy. B. MRI of the brain in a 69-year old woman seven years after diagnosis of SCLC. T_2-weighted image shows moderate cortical atrophy and the grade III periventricular and subcortical leukoencephalopathy.

Discussion

PCI was introduced in patients with SCLC on the analogy of patients with acute lymphoblastic leukemia, to reduce the incidence of brain metastases. A combined analysis of ten randomized studies assessing the impact of PCI in SCLC has shown a significant reduction in the frequency of brain metastases, from 22 percent in patients treated without PCI (PCI^-) to 6 percent in patients treated with PCI (PCI^+), although overall survival was not affected [15]. It is difficult to interpret this review since the inclusion criteria of the different studies were rather heterogeneous; patients with LD and ED as well as patients with different response rates were treated with PCI. Furthermore, the follow-up times of the studies differed. Studies with a longer follow-up time showed a higher relapse rate among PCI^+ patients than among those with a short observation period, suggesting a delay in the appearance of CNS metastases in these patients rather than a true reduction [16].

In the present non-randomized study, with a follow-up time of at least two years, brain metastases occurred more frequently in PCI^- patients, although the difference was not statistically significant. The brain metastasis-free survival in PCI^+ patients was longer than in PCI^- patients. These findings suggest at least a delay in the occurrence of brain metastases, although there was probably no reduction in the rate.

The beneficial effects of PCI seem to be more prominent in patients with durable thoracic response. In a study from the Memorial Sloan-Kettering Cancer Center, PCI significantly improved survival corrected for thoracic relapse (2-year survival PCI^+ 56%; PCI^- 14%) [8]. In our study, conversely, brain relapse as the sole site of tumor activity occurred in one PCI^+-

patient. However, our population was too small to allow conclusions on this subject.

Numerous reports have been published concerning potential side effects of PCI. Acute sequelae have been found to consist of local symptoms and signs, such as headache, nausea, skin irritation, mucositis and alopecia. Delayed effects have included CNS symptoms and signs, such as memory problems and neuroradiologic changes.

Only a few studies have described early side effects. The severity of these adverse effects was rather mild in our population. They were non-disabling and reversible without the use of medical interventions.

The rate of delayed adverse effects has been found to increase with prolonged survival and to be influenced by the timing of PCI in relation to chemotherapy. Pedersen et al. analyzed eight small studies and found various neurologic symptoms and signs in 45 percent of the PCI^+ patients. In a multicenter follow-up study of 51 long-term survivors, Van Oosterhout et al. found neurologic symptoms and signs in five of 21 patients treated with chemotherapy alone, in eight of 19 patients treated with PCI after termination of chemotherapy and in eight of 11 patients treated with PCI concurrent with chemotherapy [17]. In our population, PCI was given after termination of chemotherapy. In the present study, memory problems were seen in six of seven PCI^+ patients. The onset of neurologic deficits was within one year.

Frytak et al. found an incidence of leukoencephalopathy of 4 percent in patients surviving under 1.5 years and of 37 percent in patients surviving over 1.5 years [11]. The development of leukoencephalopathy is furthermore influenced by the timing of chemotherapy and irradiation and by the chemotherapeutics given [13]. In our study, five follow-up scans were available, revealing white matter changes in four. Atrophy was found in four patients.

We conclude that the observed benefit in overall survival and in brain metastasis-free survival in PCI^+ patients was probably an effect of PCI. However, this was a non-randomized study with a rather small number of patients. Therefore, we could not exclude the interference of other prognostic factors and the possibility that the differences in survival could well be due to chance. Large-scale randomized studies would allow more definite conclusions.

Side effects were prominent in patients treated with PCI. The rate of possibly treatment-related side effects in our study was high in comparison to those mentioned in the literature. This could partly be explained by the strict neurologic follow-up scheme and by the more accurate imaging techniques used.

Our findings confirm earlier studies which found that PCI may be effective by decreasing the frequency of brain metastases and by increasing the brain metastasis-free survival and overall survival, with a minor risk of clinical and radiologic neurotoxicity.

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