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## Original Paper

# Prophylactic Cranial Irradiation in Limited Stage Small Cell Lung Cancer: Survival Benefit in Patients with Favourable Characteristics

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**The value of prophylactic cranial irradiation (PCI) in the treatment of small cell lung cancer (SCLC) remains controversial. As part of a randomised study investigating the timing of chest irradiation (CI) with respect to combination chemotherapy, the effect of PCI was evaluated. Between 1981 and 1989, patients were randomised to initial chest irradiation ICI (99 patients) or 18 weeks delayed late chest irradiation LCI (100 patients). PCI was given to 157 patients. In the beginning, only ICI patients received PCI, but in October 1984 the strategy was changed so that all patients received PCI. Thus, the patients who did not receive PCI were randomly allocated. The PCI dose was 33 Gy/11 fractions (45 patients) and 25 Gy/11 fractions (112 patients). The 2-year CNS-recurrence rate (± standard error) was significantly lower in patients who received PCI, 16.3 ± 4.1%, than in those who did not, 55.1 ± 12.4% ($p = 0.01$). In contrast, the 2-year cause-specific survival was not significantly different, 24.9 ± 3.6% and 16.9 ± 6.2% ($p = 0.31$). The 2-year progression-free rates with or without PCI were 18.5 ± 3.3% and 11.4 ± 5.4%, respectively ($p = 0.58$). To test the hypothesis that a benefit from PCI would mainly be expected among the patients with the best prognosis, a multivariate regression analysis of prognostic factors was undertaken. Based on weight loss, performance status, serum sodium and age, the third of the patients with the best prognosis were identified. In that group of patients, the survival advantage from PCI was statistically significant, 35.5 ± 7.2% versus 14.1 ± 8.0%, $P = 0.029$. These results are currently being tested in a Danish multicentre trial where patients with a good prognosis are randomised either to receive PCI or not to receive PCI.** 

**Key words: small cell lung cancer, limited stage, prophylactic cranial irradiation, prognostic factors, CNS metastases, long-term survival**

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## INTRODUCTION

Approximately 20% of all primary malignancies of the lung are classified as small cell lung cancer (SCLC). This subtype is known to be very sensitive to chemotherapy as well as to radiotherapy [1]. Complete response to chemotherapy is seen in 50–60% of the patients with limited disease (LD), compared to 15–25% of the patients with extensive disease (ED). However, long-term survival is only obtained in a very small proportion of the patients and primarily in those classified as having LD. The 2-year survival is approximately 20% for LD and 2% for ED, whereas the 5-year survival is even lower, 7% for LD and 1% for ED [2–4].

At autopsy, CNS metastases can be demonstrated in 50% of patients with SCLC to whom prophylactic cranial irradiation (PCI) had not been administered [5–8], and it can be concluded that systemic chemotherapy does not effectively prevent CNS recurrences. CNS involvement is an important cause of morbidity and mortality in patients with SCLC [9], and several studies have, therefore, investigated the possibility of reducing the incidence of CNS recurrences [10, 11]. However, the majority of these studies have been retrospective.

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Although a number of randomised controlled trials have been conducted, most of these include only a limited number of patients. Thus, it remains controversial whether a reduced CNS relapse rate from PCI will increase the overall survival and/or the time to progression [12, 13]. In addition, many centres have been reluctant to use PCI due to toxicity [10, 14].

Here, the effect of PCI was evaluated as a part of a randomised trial on the timing of radiotherapy and chemotherapy in LD SCLC. These data have been used to evaluate the effect of PCI on the CNS recurrence rate, the overall survival and the toxicity.

## PATIENTS AND METHODS

From 1981 to 1989, a prospective study was conducted with the aim of evaluating the timing of chest irradiation in relation to chemotherapy. In this analysis, only the effect of PCI will be evaluated, whereas the aspects of the timing of chest irradiation will be reported separately. The criteria for eligibility were histologically documented LD SCLC, age <70 years, Karnofsky index ≥40%, no other primary cancer, no prior radiotherapy and/or chemotherapy, no prior surgical resection of primary tumour and informed consent.

LD SCLC was defined as disease confined to only one lung, hili, mediastinum or supraclavicular nodes. Patients with invasion of the trachea or the contralateral main bronchus were also included. Invasion of the contralateral supraclavicular nodes were defined as ED. The staging procedures included history and physical examination, haematological and chemical profiles, chest radiography and bone scintigraphy. In addition, bone marrow aspiration and biopsy from sternum and iliac crest as well as computer tomography (CT)-scan or ultrasound of the abdomen were carried out. CT-scan of the brain, lumbar puncture or other diagnostic procedures were performed only when indicated.

All patients received the same chemotherapy regimen and were randomised to either initial chest irradiation (ICI) or late chest irradiation (LCI) (Figure 1). In the beginning, PCI was only given to patients randomised to ICI, but after October 1984 the treatment strategy was changed, so that all patients received PCI independent of the timing of the chest irradiation. This change was introduced because reports in the literature had indicated that PCI could improve the overall treatment result in SCLC. PCI was always given initially either together with ICI or, in the LCI arm, together with the first cycle of chemotherapy. PCI was given as whole brain irradiation with parallel opposing lateral fields using $^{60}$Co.

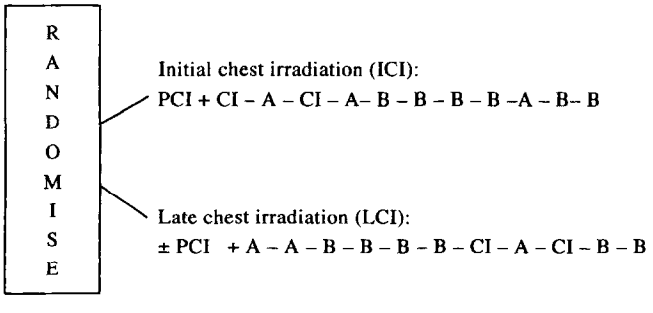


**Figure 1. Treatment schedules according to randomisation. A: cisplatin 60 mg/m², i.v. (day 1) + etoposide 120 mg/m², i.v. (days 4, 6, 8); B: cyclophosphamide 1000 mg/m², i.v. (day 1) + doxorubicin 45 mg/m² i.v. (day 1) + vincristine 1.4 mg/m², i.v. (day 1).**

Initially, the dose was 33 Gy/11 fractions/1 fraction per day. However, mid way in the study the dose was lowered to 25 Gy/11 fractions in order to reduce the risk of neurological sequelae. A total of 112 patients were planned to receive 25 Gy, but only 103 patients received the planned dose. 4 patients did not start PCI, 1 because of progressive disease (PD), and 3 had PCI postponed because of poor general condition. The other reasons for deviation from the planned dose was pause in radiotherapy (1), error in the dose (1), CNS recurrence during PCI (2), and sudden intercurrent death (1). 45 patients were planned to receive 33 Gy and only one of these received a lower total dose because of poor general condition.

The treatment field of chest irradiation included the ipsilateral hilum and the bilateral mediastinum and the field size was outlined based on chest X-ray. The supraclavicular nodes were only included if this region was involved. Chest irradiation was given with opposing fields using 8–16 MV photons. Initial chest irradiation was given as a split-course treatment, i.e. two treatment periods of 20–22.5 Gy/11 fractions/1 fraction per day separated by an interval of 14 days in which chemotherapy was given (Figure 1). Late chest irradiation was given in the same way after the patients had received six cycles of chemotherapy. Apart from the periods of irradiation all patients received nine cycles of chemotherapy at 3 week intervals as shown in Figure 1.

Response to treatment was evaluated from a chest X-ray according to the WHO criteria. Patients who died of disease, before a follow-up chest X-ray was taken, were classified as having PD. Patients who died before or within 1 week after the start of treatment were classified as not evaluable.

The scheduled follow-up period was 5 years after diagnosis. In general, patients were followed at 3–4 months intervals with physical examination and chest X-ray. Late toxicity symptoms in patients were evaluated retrospectively from chart information.

*Endpoints and statistical analysis*

Time to maximum local response, relapse and survival were measured from the date of randomisation, which in most patients was identical with the first day of treatment. CNS recurrence-free and progression-free rates were both measured from date of randomisation to the date when recurring disease was verified. Cause-specific survival was survival until death of/or with SCLC or death of treatment related complications. Actuarial estimates of survival in subgroups of patients were obtained by the product-limit method of Kaplan and Meier [15]. When comparing two groups only, the Mantel–Cox logrank test [16] was used to test for a difference in survival rate. In case of more than two groups, a test-for-trend [17] based on the logrank test was used.

Multivariate regression analysis of time-to-death from any cause was performed using Cox's proportional hazards model [18]. A graphical test of the proportional hazards assumption was performed as described by Bentzen and associates [19]. A possible deviation from a log-linear relationship between the value of specific clinical characteristics and the hazard rate was tested by including the value of the covariate and the square of this value in a forward selection of prognostic factors. In no case did the inclusion of the squared value produce a significant improvement in the log likelihood. The prognostic strength of a particular clinical characteristic was quanitified by the ratio of hazard rates corresponding to an increase of 1

*Table 1. Clinical characteristics of patients treated with and without PCI*

| | +PCI (%) | −PCI (%) | Total |
|---|---|---|---|
| Number of patients (%) | | | |
| ICI | 99 (63.1) | 0 | 99 |
| LCI | 58 (36.9) | 42 (100.0) | 100 |
| Total | 157 | 42 | 199 |
| Performance status Karnofsky index | | | |
| 100 | 18 (11.5) | 5 (11.9) | 23 (11.6) |
| 90–80 | 114 (72.6) | 24 (57.2) | 138 (69.3) |
| 70–60 | 20 (12.7) | 9 (21.4) | 29 (14.6) |
| 50–40 | 5 (3.2) | 4 (9.5) | 9 (4.5) |
| Total | 157 (100.0) | 42 (100.0) | 199 (100.0) |
| M:F ratio | 1.5:1 | 2.5:1 | 1.6:1 |
| Median age (years) | 61 | 59 | 60 |
| Age range (years) | 36–70 | 36–69 | 36–70 |

ICI, initial chest irradiation; LCI, late chest irradiation; PCI, prophylactic cranial irradiation.

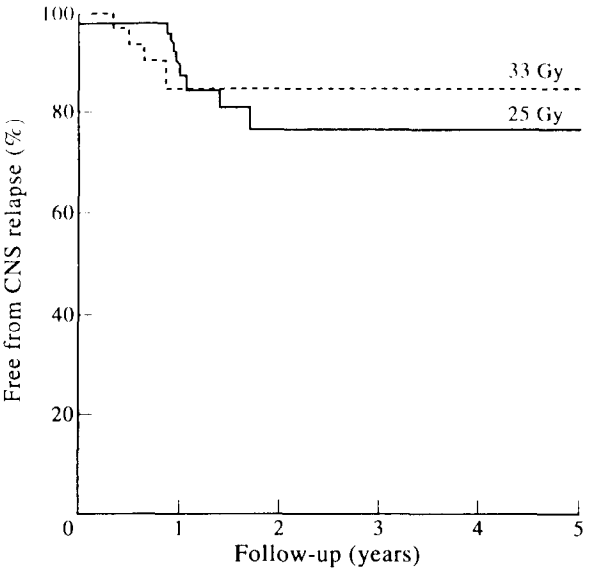


**Figure 2. Actuarial estimate of the CNS recurrence-free rate depending on whether the PCI dose was 33 Gy ($n = 45$ patients) or 25 Gy ($n = 112$ patients).**

standard deviation of the distribution of the characteristic in question.

## RESULTS

199 patients with limited-stage small cell lung cancer (LD SCLC) were eligible and entered the study. All patients were referred to and treated within the oncology centre in Aarhus. Approximately 85% of all referred patients with LD SCLC went on to trial, the remaining 15% did not fulfill the eligibility criteria. By randomisation, 99 patients received ICI and 100 patients received LCI. Table 1 shows the distribution of the timing of chest irradiation, sex, age and performance status in the two groups of +PCI and −PCI. Table 2 shows the response to treatment after the various treatment regimens. 2 patients were not evaluable due to early death, one was randomised to LCI with PCI, and one to LCI without PCI.

*Table 2. The response to treatment between the groups receiving initial chest irradiation (ICI) or late chest irradiation (LCI) and patients treated with and without PCI*

| | Response* number of patients (%) | | | | |
|---|---|---|---|---|---|
| Treatment | CR | PR | NC | PD | Total |
| ICI | 58 (58.6) | 30 (30.3) | 5 (5.0) | 6 (6.1) | 99 (100.0) |
| LCI | 60 (61.2) | 23 (23.5) | 10 (10.2) | 5 (5.1) | 98 (100.0) |
| +PCI | 93 (59.6) | 43 (27.6) | 11 (7.0) | 9 (5.8) | 156 (100.0) |
| −PCI | 25 (61.0) | 10 (24.4) | 4 (9.7) | 2 (4.9) | 41 (100.0) |
| All patients | 118 (59.9) | 53 (26.9) | 15 (7.6) | 11 (5.6) | 197 (100.0) |

PCI, prophylactic cranial irradiation.
*WHO criteria.

As can be seen, CR was achieved in 58.6% of patients receiving ICI, and in 61.2% receiving LCI. For those who received PCI, 59.6% achieved CR compared to 61.0% of those who did not receive PCI. There was no significant difference in response between the two groups. Evaluation of response was not possible in 2 patients, as they either died before or shortly after treatment was started.

45 patients received a total dose of 33 Gy and 112 patients a dose of 25 Gy. The CNS recurrence-free rate as a function of dose is shown in Figure 2. The 5-year incidence of CNS recurrences was 14.9 ± 7.0% and 22.9 ± 6.6% after 33 Gy (112 pts) and 25 Gy (45 pts), respectively. This difference was not statistically significant.

A total of 157 patients received PCI. There was no significant difference in the CNS recurrence rate between the groups ICI and LCI, neither when studying all 157 patients nor when studying the 118 patients achieving CR in the chest (Table 3). As seen from Table 3, PCI gave a highly significant reduction in the incidence of CNS recurrences both in all patients and in those obtaining CR. Yet, the progression-free rate and cause-specific survival after 2 years did not differ in the two groups (+PCI and −PCI, Table 4). The crude CNS relapse rate was 9.6% (15/157 patients) for those who received PCI and 31.0% (13/42 patients) for those who did not receive PCI.

*Table 3. Two year incidence of CNS recurrences*

| 2-year incidences of CNS recurrences | +PCI | −PCI | ICI | LCI |
|---|---|---|---|---|
| All patients | 16.3% (± 4.1%)* | 55.1% (± 12.4%) | 19.2% (± 5.5%) | 28.4% (± 6.7%) |
| Patients obtaining CR | 13.0% (± 4.4%) | 58.2% (± 14.5%) | 15.9% (± 6.0%) | 25.3% (± 7.6%) |

PCI, prophylactic cranial irradiation; ICI, initial chest irradiation; LCI, late chest irradiation.
*± Standard error.

*Table 4. Progression-free rate and cause-specific survival after 2 and 5 years for the groups treated with and without PCI*

| Rate/survival | +PCI | −PCI |
|---|---|---|
| 2-year progression-free rate | 18.5% (± 3.3%)* | 11.4% (± 5.4%) |
| 5-year progression-free rate | 15.1% (± 3.1%) | 7.6% (± 4.4%) |
| 2-year cause-specific survival | 24.9% (± 3.6%) | 16.9% (± 6.2%) |
| 5-year cause-specific survival | 16.5% (± 3.1%) | 10.2% (± 5.0%) |

PCI, prophylactic cranial irradiation.
*± Standard error.

The 2-year incidence of distant metastases outside the CNS was 46.8 ± 5.3% for +PCI and 40.0 ± 13.5% for −PCI, respectively. The 5-year incidence was 54.8 ± 5.9% after PCI and 40.0 ± 13.5% without PCI. This difference was not statistically significant.

A number of clinical characteristics were included in a multivariate regression analysis using the Cox proportional hazards model with death from any cause as the endpoint. The following 11 prognostic factors were tested: sex, age, performance status, weight loss, haemoglobin concentration, serum sodium, serum potassium, serum lactate dehydrogenase (LDH), ±PCI, ICI/LCI, and clinical stage. 187 patients were included in the analysis. In 12 patients one or more of the prognostic factors were missing and they were therefore not included in the analysis. Among the factors, performance status, weight loss, serum sodium, and patients' age had a significant influence on overall survival. For each of these covariates, relative risks were estimated for an increment corresponding to 1 standard deviation of the distribution of that covariate. Using the regression coefficients from Table 5, a prognostic index was calculated for each patient, based on the patient's performance status, serum sodium, weight loss and age. The patients were grouped according to the 33% percentiles of the distribution of this index. Figure 3 shows the effect of PCI on the cause-specific survival in the third of the patients with the best prognosis. There was a significant difference in 5-year survival between those receiving PCI (35.5 ± 7.2%) and those that did not receive PCI (14.1 ± 8.0%; $P = 0.029$), as well as immediate cause-specific survival (with PCI, 20.7 months; without PCI 13.1 months).

*Table 5. Cox's proportional hazards model of prognostic factors for death from SCLC*

| | Covariate | | | |
|---|---|---|---|---|
| Prognostic factors | β | SE (β) | RR (95% CI) | *P*-value |
| Performance status | −0.019 | 0.007 | 0.83 (0.72, 0.95)* | 0.008 |
| Serum sodium | −0.049 | 0.018 | 0.78 (0.65, 0.93)† | 0.010 |
| Weight loss | 0.029 | 0.014 | 1.19 (1.01, 1.40)‡ | 0.005 |
| Age | 0.033 | 0.013 | 1.26 (1.05, 1.51)§ | 0.011 |

β, regression coefficient; SE(β), standard error of the regression coefficient; RR, relative risk estimated for *an increase of 10 points in Karnofsky performance status; †an increase of 5 mmol/l in serum sodium; ‡6 kg of weight loss; and §7 years of age. 95% CI, 95% confidence interval.

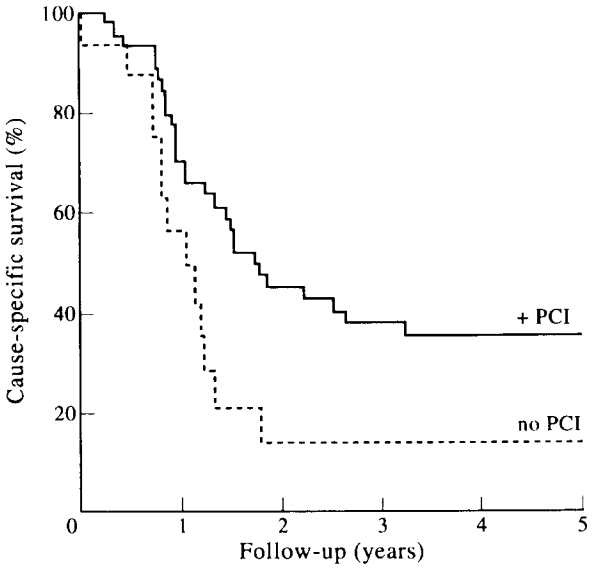


**Figure 3. Survival of the one third of the patients with the best prognosis depending on whether PCI was given ($n = 46$) or not ($n = 16$).**

To test whether this difference in survival could be attributed to an improved control in the CNS, the incidence of distant metastases outside the CNS were compared in the two groups. The 5-year incidence was 34.0 ± 8.0% in the PCI group and 56.7 ± 18.5% in the group not receiving PCI. The difference was not statistically significant ($P = 0.39$).

Early toxicity was minimal, although varying headache and mild nausea were registered during PCI. No major toxicity was seen during the treatment. Symptoms which could be related to CNS toxicity were evaluated blindly in all patients. 10 patients had such symptoms, and details of these are shown in Table 6. Based on charts, the symptoms were graded retrospectively according to the EORTC system. There was no difference in the frequency and severity of toxicity between the patients receiving or not receiving PCI. None of the aforementioned symptoms were present before the beginning of treatment, and in several cases the symptoms disappeared or weakened over time. None of the patients were examined by a neurologist.

## DISCUSSION

For more than 10 years, the value of PCI has been debated. Several prospective and retrospective studies have been carried out, but still the routine use of PCI is controversial [20–22].

In this study, the CNS-recurrence rate was significantly reduced after PCI in all patients and in the subgroup of 118 patients obtaining CR. This is in agreement with several other studies [23, 24]. In the present study, two different doses of PCI were given and there was no statistically significant difference ($P = 0.97$) in the incidence of CNS recurrences between the two doses.

Concerning the timing of chest irradiation, there was no difference in the CNS recurrences whether chest irradiation was given at the beginning of treatment or with a delay of 16 weeks. This is in contrast to the findings by Murray and associates [25], who found that a delay of 12 weeks regarding initiation of chest irradiation was associated with a significant increase in the incidence of CNS recurrences. The combi-

*Table 6. Late neurotoxicity, which could be related to PCI. Evaluated blindly and retrospectively based on charts information*

| PCI | Dose (Gy) | Age at diagnosis | Sex | Symptoms starting months after diagnosis | Symptoms | EORTC* scoring system grade 0–4 | CT scanning/autopsy | Competing diseases | Died months after diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| + | (25) | 68 | M | 4 | Severe parasthesias of fingers | Sensory toxicity gr. 3 | Never performed | | 13 |
| + | (25) | 54 | F | 12 | Decreased recent memory, mild confusion | Cortical toxicity gr. 2 | CT scan without metastases, slight cortical atrophy | | 21 |
| + | (33) | 53 | F | 6 | Flittering scotoma, decreased co-ordination of legs | Visual change gr. 1<br>Headache gr. 1<br>Cerebellar toxicity gr. 1 | CT scan and autopsy without metastases | | 7 |
| + | (33) | 61 | M | 6 | Weakness of legs, periodically confused | Motor toxicity gr. 2<br>Cortical toxicity gr. 1 | Slight atrophy, could not exclude metastases | Through 7 years angina pectoris | 9 |
| + | (33) | 62 | F | 8 | Went almost blind, weakness of legs | Visual change gr. 3<br>Motor toxicity gr. 3 | Was never performed because patient died | Disseminated arteriosclerosis | 9 |
| + | (33) | 55 | F | 9 | Moderate parasthesias of hands and feet | Sensory toxicity gr. 2 | Was never performed, patient died of cerebral haemorrhage | Raynaud phenomenon | 102 |
| − | 0 | 48 | M | 5 | Moderate parasthesias of hands and feet, sensory loss | Sensory toxicity gr. 2 | Never performed | | 11 |
| − | 0 | 56 | M | 4 | Severe parasthesias of hands and feet | Sensory toxicity gr. 3 | Autopsy with CNS metastases | | 22 |
| − | 0 | 61 | M | 5 | Parasthesias of feet and loss of sensory | Sensory toxicity gr. 2 | Never performed | Morbus cordis incomp. | 12 |
| − | 0 | 61 | M | 2 | Slight unco-ordination of hands, weakness of legs | Cerebellar toxicity gr. 2<br>motor toxicity gr. 2 | Autopsy without metastases, died of pulmonary abscess | | 6 |

*EORTC scoring system. gr. 0, no symptoms; gr. 1, mild symptoms; gr. 2, moderate symptoms; gr. 3, severe symptoms; gr. 4, life threatening symptoms.

nation of drugs, the PCI doses and the response rates are almost identical with those employed in our study. PCI was given at the end of the treatment (21 weeks delayed) in contrast to our study where PCI was given from the beginning. This difference in timing of PCI with respect to chest irradiation and chemotherapy could be a possible explanation for the different results in the two studies.

Toxicity has been the argument against PCI, especially in the absence of a demonstrable improvement in survival. In our study, the toxicity was acceptable. However, our data were based on retrospective chart information. Only 10 patients had CNS symptoms which could be related to PCI. As the charts were evaluated blindly, it was discovered that only 6 of the 10 patients actually received PCI. Competing diseases, subclinical brain metastases and the chemotherapy regime consisting of both vincristine and cisplatin may have caused some of the symptoms. Based on these data, toxicity related to CNS was distributed equally in our study between the two groups (+/−PCI). Other studies have also shown a modest toxicity after PCI. Lishner and associates [26] retrospectively analysed 58 long-term survivors and found that 9 out of 48 patients receiving PCI had neurological complications, but in only 2 of those did PCI seem to be responsible. Chemotherapy and underlying diseases were probably contribute significantly to the complications. Seydel and colleagues [24] found only 3 patients with CNS symptoms among 45 who survived 1 year after PCI. In the future, randomised trials evaluating quality of life and neurological status before and after PCI should be conducted in order to evaluate the sequelae of PCI.

A significant difference in overall survival after PCI has never been demonstrated. One explanation could be that the majority of SCLC patients will die from disseminated disease before a benefit in survival from PCI becomes apparent. Thus, we hypothesised that a benefit from PCI should be sought among patients who were selected by means of a prognostic model as having a relatively long life expectancy. Four prognostic factors, performance status, weight loss, serum sodium, and age, were found to be significant in a multivariate prognostic model. From individual values of these characteristics, a prognostic index was calculated for each patient, and this was used to select the one third of the patients with the best prognosis. Among these patients, PCI gave a significant gain in cause-specific survival. In other studies, many factors have been analysed to see if they were predictive for treatment outcome. Several studies have shown that performance status and serum sodium are important prognostic factors [27, 28]. This was confirmed in our analysis and, in addition, weight loss was identified as a significant prognostic parameter, even after inclusion of performance status in the prognostic model. Age was significant, which would be expected since the endpoint of the analysis was death from any cause. LDH has in several studies been shown to be of prognostic importance [28, 29], but was not significant in our analysis.

The present study suggests that if the aim is to reduce the incidence of CNS recurrences then all patients should have PCI, whereas if the aim is to improve survival then only patients with a favourable prognosis should receive PCI. A randomised trial, in which patients are selected on the basis of their prognostic index and randomised to +/− PCI, has been initiated in Denmark.


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