Original Study

Treatment Response and Prophylactic Cranial Irradiation Are Prognostic Factors in a Real-life Limited-disease Small-cell Lung Cancer Patient Cohort Comprehensively Staged With Cranial Magnetic Resonance Imaging

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Abstract

To evaluate the effect of prophylactic cranial irradiation (PCI) in patients with disease that responded to therapy, we reviewed 184 limited-disease small-cell lung cancer patients comprehensively staged by contrast-enhanced cranial magnetic resonance imaging. Treatment response and PCI strongly correlated with prolonged overall survival, time to progression, and brain metastasis–free survival.

Introduction: Prophylactic cranial irradiation (PCI) has proven to decrease the incidence of brain metastases (BMs), with a modest improvement in survival. **Patients and Methods:** The impact of PCI was evaluated in 184 patients treated with chemoradiotherapy. PCI was applied to patients with disease with partial and complete response only when cranial magnetic resonance imaging before and after primary treatment revealed no BMs. Correlation between PCI and overall survival (OS), BM-free survival (BMFS), and time to progression (TTP) was analyzed to describe survival within subgroups. **Results:** Concurrent and sequential chemoradiotherapy was applied in 71 patients (39%) and 113 patients (61%), respectively. Seventy-one patients (39%) with partial and complete response were treated with PCI. Metachronous BMs were detected in 16 (23%) of 71 patients in the PCI group compared to 42 (37%) of 113 patients in the non-PCI group. Median BMFS in the PCI group was not reached; it was 23.6 months in the non-PCI group. Median OS and TTP were 26 months (range, 19.4-32.6 months) in the PCI group versus 14 months (range, 11.4-16.6 months) in patients without PCI whose disease responded to therapy versus 9 months in patients with disease that did not respond to therapy ($P < .0001$), and 27 versus 14.5 months (range, 9.0-19.9 months) versus 8.8 months (range, 7.7-9.9 months) ($P < .0001$) in the PCI group versus those with response without PCI versus those with nonresponse. The effect of PCI was independent of gender. On multivariate analysis, PCI was a variable correlating with OS (hazard ratio = 1.899; 95% confidence interval, 1.370-2.632; $P < .0001$) and TTP (hazard ratio = 2.164; 95% confidence interval, 1.371-3.415; $P = .001$) after adjustment for other prognostic factors. **Conclusion:** In real-life patients comprehensively staged with cranial magnetic resonance imaging, treatment response and PCI strongly correlated with prolonged OS, TTP, and BMFS.

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Introduction

Small-cell lung cancer (SCLC) accounts for about 13% of all lung cancer cases[1] and is characterized by early dissemination and high sensitivity to chemotherapy and radiotherapy.[2-4] SCLC has a strong tendency to metastasize to the brain. About 10% of the patients initially present with brain metastases (BMs). The 2-year cumulative risk rises to $\geq$ 50%,[5] and BMs are found in up to 80% of SCLC patients at autopsy.[6]

Because the blood–brain barrier has been considered to protect the central nervous system from cytotoxic agents, the role of prophylactic cranial irradiation (PCI) has been extensively studied.[7-10] Schild et al[8] demonstrated that PCI was associated with a significant survival benefit for both limited-disease (LD) and extensive-disease SCLC patients who had stable disease or better response to chemotherapy with or without thoracic radiotherapy (TRT). In addition, a study by Rule et al[10] using the same pooled data demonstrated that PCI was associated with a significant improvement in survival for the entire elderly SCLC patient cohort on univariate analysis.

A review of retrospective data on PCI suggested that prolongation of OS would be restricted to the patients in complete remission because those with residual extracranial disease die promptly from systemic cancer progression.[11] Another retrospective analysis suggested that the gain in survival was restricted to patients with locally advanced disease stage (International Union Against Cancer [UICC] II-IIIB).[12] In 1999, Aupérin et al[9] showed in a meta-analysis of PCI for SCLC patients with complete remission after induction therapy that the relative risk of death in the PCI group versus the control group was 0.84 (95% confidence interval [CI], 0.73-0.97; $P = .01$), which corresponds to a 5.4% increase in the rate of survival at 3 years (15.3% in the control group vs. 20.7% in the treatment group). PCI also increased the rate of disease-free survival (relative risk of recurrence or death, 0.75; 95% CI, 0.65-0.86; $P < .001$) and decreased the cumulative incidence of BM (relative risk, 0.46; 95% CI, 0.38-0.57; $P < .001$). Previously we found a significant prevalence of BMs in LD SCLC patients with complete response immediately after completion of primary treatment and recommended a second cranial magnetic resonance imaging (cMRI) study as a routine diagnostic tool before application of PCI.[13] A recently published retrospective study from Ozawa et al[14] suggested that PCI may be less beneficial in patients with LD SCLC when continuous management with cMRI and stereotactic radiosurgery as a treatment option are permanently available.

To evaluate the exact impact of PCI on survival in a real-life patient cohort treated with chemoradiotherapy (CRT), we retrospectively analyzed the medical charts of 184 LD SCLC patients who were comprehensively staged with cMRI at initial diagnosis and immediately before application of PCI.

Patients and Methods

From 1998 to 2012, 184 patients from 2 institutions in Germany were diagnosed with LD (UICC stage I-III) SCLC. Diagnosis was confirmed histologically. LD consisted of patients with disease confined to a single hemithorax with or without contralateral mediastinal and ipsilateral supraclavicular lymph node involvement.[15] Patients with pleural effusion and involvement of the contralateral supraclavicular and/or hilar lymph nodes were excluded from the analysis.[16] Initial staging consisted of computed tomographic (CT) scans of the chest and abdomen, bone scintigraphy, bronchoscopy with biopsy, and first cMRI. All patients received definitive CRT concomitantly or sequentially. Before treatment, all patients provided written informed consent. The university's ethics committee approved this retrospective study.

Before 2005, sequential CRT was provided as per institutional policy. Seventy-one patients (39%) received concomitant CRT consisting of TRT starting with the first or second cycle of chemotherapy followed by 2 to 4 consolidation cycles, while 113 patients (61%) received sequential CRT, defined as 4 to 6 cycles of chemotherapy followed by TRT. TRT was delivered on LINAC with multiple coplanar 6 to 15 MV beams. Three-dimensional CT-simulated treatment planning was performed. Planning target volume was defined as initial primary tumor and involved lymph nodes (short axis > 1 cm on pretherapeutic CT) with a 1.0 cm margin. A total of 96% patients were treated 5 days a week with 1.8 to 2.0 Gy daily fractions to a total dose of at least 54.0 Gy (range, 54.0-66.0 Gy). Four percent of patients were treated with hyperfractionated accelerated TRT according to Turrisi et al.[17] On completion of CRT, response evaluation was performed within 2 weeks based on CT scans (thorax and abdomen) and bone scintigraphy. A second cMRI was routinely performed in patients with disease that partially or completely responded to therapy before commencing PCI to exclude BM. A total of 71 patients (39%) were treated with PCI (2 simulated opposite fields with daily fraction of 2.0 Gy to a total dose of 30.0 Gy). Thereafter, patients were followed every 3 months during the first 2 years and every 6 months for the third year from the end of multimodal therapy until death.

All patients were registered until death or loss to follow-up. Survival rates were analyzed according to the Kaplan-Meier method and were measured from the date of initial diagnosis by SPSS 16.0 software (IBM SPSS). Kaplan-Meier analyses were used to compare survival curves for the PCI and non-PCI subgroups. Application of PCI to those with disease that responded to therapy was analyzed for its association with overall survival (OS) and time to progression (TTP) by univariate and multivariate Cox regression. A 2-sided error level of $P < .05$ was considered statistically significant. Variables significantly associated with OS in the univariate analysis were entered into a multivariate analysis. TTP was defined as the length of time from the date of diagnosis until the disease worsened or spread to other parts of the body. Hence, TTP theoretically differed from progression-free survival in that the event of interest was only disease progression.[18]

Results

One hundred eighty-four patients were treated with definitive CRT. Patient and treatment characteristics are listed in Table 1. One hundred eleven (60%) were men and 73 (40%) were women. Median age at diagnosis was 63 years (range, 34-83 years). Median performance status according to the World Health Organization classification for the entire cohort was 1 (range, 0-3). Mediastinal lymph node involvement was documented in 110 patients (60%). A total of 101 patients (55%) had stage T3/4 disease. Seventy-one patients (39%) were treated in the concurrent and 113 (61%) in the sequential setting. There were no significant differences with in regard to age, sex, performance status, and tumor, node, metastasis