Original Study

Usage of Prophylactic Cranial Irradiation in Elderly Patients With Small-cell Lung Cancer

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Abstract

Little is known about the contemporary use of prophylactic cranial irradiation (PCI) in elderly patients with small cell lung cancer. Data from the Netherlands Cancer Registry on patients treated with chemotherapy or chemoradiotherapy from 2009 to 2013 revealed that the PCI usage rate was 74% for stage I to III and 41% for stage IV. The use of PCI decreased with advancing patient age.

Background: Prophylactic cranial irradiation (PCI) reduces the risk of overt brain metastases in patients with small-cell lung cancer (SCLC) and is currently recommended in guidelines for both limited and extensive disease. Given the concerns about the greater frequency of neurologic side effects in elderly patients, we studied the association among age, PCI usage, and survival for SCLC patients in the Netherlands. **Patients and Methods:** Data from the Netherlands Cancer Registry for patients diagnosed with SCLC from 2009 to 2013 were queried. Separate analyses were performed for patients with stage I to III, treated with chemoradiotherapy (n = 1684) and patients with stage IV, treated with chemotherapy or chemoradiotherapy (n = 3481). Patients with brain metastasis at diagnosis were excluded. **Results:** For patients with stage I to III, the overall PCI usage rate was 74%, and the rate decreased with age, from 78% for patients aged 18 to 59 years to 66% for patients aged ≥ 80 years. For patients with stage IV, the overall PCI usage rate was 41% and decreased with age, from 46% for patients aged 18 to 59 years to 23% for patients aged ≥ 80 years. Gender and socioeconomic status did not affect the PCI rates. For patients aged < 70 years and treated with PCI, the median survival was 45, 24, and 12 months for stage I and II, III, and IV, respectively. For patients aged ≥ 70 years treated with PCI, the corresponding survival duration was 33, 17, and 10 months. **Conclusion:** In the Dutch population, PCI usage rates were fairly high but were significantly lower for elderly patients.

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Introduction

Small-cell lung cancer (SCLC) comprises 15% of all lung cancers and carries a poor prognosis, with 7% surviving at 5 years from diagnosis. Brain metastases occur frequently in patients with SCLC; however, this can be reduced by prophylactic cranial irradiation (PCI).[1] In patients with nonmetastatic disease, treatment involves platinum-based chemotherapy and thoracic radiotherapy, followed by PCI.[2] In 1999, a meta-analysis of 987 patients who had achieved complete remission on chest radiographic examination revealed that PCI more than halved the occurrence of brain metastases and improved the 3-year survival rate from 15.3% to 20.7%.[3] In 2007, a European Organization for Research and Treatment of Cancer trial of 286 patients with extensive SCLC disease and any response to chemotherapy reported that PCI reduced the occurrence of symptomatic brain metastases from 41.3% to 16.8% and improved the median overall survival from 5.4 months to 6.7 months.[4] Consequently, the current international guidelines also recommend PCI for extensive disease.[5,6]

However, limited information is available about the actual usage rates of PCI at a population-based level. PCI could be withheld in the case of an insufficient response to induction treatment or because of poor performance status or neurocognitive status. Patients could also refuse PCI because of concerns about potential toxicity,[7] notwithstanding that the neurotoxic effects were mainly seen with concurrent chemotherapy and high fraction doses and could not be confirmed in studies with dose-fractionation schedules of 25 Gy in 10 fractions.[8,9] Reflection about the pros and cons of

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PCI is warranted for treatment decisions in the elderly population, mainly because neurocognitive complications tend to be more common at older ages.[10] Information about the benefits of PCI in elderly patients is rather limited, because elderly patients have been underrepresented in clinical trials.[2] Patients' life expectancy should be considered because chronic neurotoxicity will have a lasting effect in patients with a favorable prognosis.

Given these considerations, the main objectives of our study were to assess the effect of age and other determinants on the usage of PCI in the Netherlands and to explore recent survival outcomes for SCLC patients who received PCI. We did not assess the effect of PCI on survival because of the impediments of selection bias and immortal time bias,[11] which imply that the real benefit of PCI can only be determined in randomized comparisons.

Patients and Methods

Data from patients with primary SCLC diagnosed from 2009 through 2013 was retrieved from the Netherlands Cancer Registry (NCR), after formal approval by the NCR monitoring committee. The NCR collects data on all cancer cases diagnosed in the Netherlands, based on notification of newly diagnosed malignancies by the national automated pathologic archive and hospital discharge diagnoses. Information on the diagnosis, staging, and treatment is extracted routinely from the medical records by specially trained NCR personnel. Information on survival status is updated annually using a computerized link with the national civil registry. For the present analysis, survival information was updated to January 1, 2015. Cause of death information was not available because of privacy regulations.

Stage information was recorded using the sixth edition (2009) or seventh edition (2010-2013) of the TNM Classification of Malignant Tumors from the International Union Against Cancer. The sites of distant metastasis at diagnosis were recorded using the topography codes of the International Classification of Diseases for Oncology, third edition. For patients with stage I to III, our analysis was restricted to those who had undergone a combination of chemotherapy and thoracic radiotherapy, including both concurrent and sequential schedules. For patients with stage IV disease, the analysis was restricted to those who had undergone chemotherapy, with thoracic radiotherapy optional. Patients with synchronous or metachronous lung tumors or brain metastasis at diagnosis were excluded from the analysis. Data about comorbidity and performance status were not available. Socioeconomic status was inferred from the postal code and quantified in quintiles.

Treatment information included coding for thoracic radiotherapy, chemotherapy, and PCI. Specifics regarding the type of chemotherapy, number of cycles, dose-fractionation schedule of radiotherapy, and brain staging examinations were not available. Chemotherapy and chemoradiotherapy doses could have been incomplete owing to toxicity or early progression. Information on the treatment response after chemotherapy and chemoradiotherapy was not available.

The Dutch national guideline recommends PCI for patients with a complete or partial response or stable disease after chemoradiotherapy for stage I to III SCLC. The preferred chemotherapy schedule comprises 4 cycles of cisplatin-etoposide. PCI is also recommended for patients with any response or stable disease after chemotherapy for stage IV disease. The preferred chemotherapy schedule comprises 4 to 6 cycles of cisplatin-etoposide. PCI should be started within 60 days of the last day of chemotherapy administration, and the preferred schedule was 10 fractions of 2.5 Gy. Adjuvant thoracic radiotherapy could have been applied in connection with the CREST (Radiation Therapy to Prevent Brain Metastases in Patients With Previously Treated Extensive-Stage Small Cell Lung Cancer) trial (ClinicalTrials.gov identifier, NCT00016211), which accrued patients from 2009 to 2012.[12] Only a few patients were treated with hippocampal avoidance PCI related to a randomized phase III trial (ClinicalTrials.gov identifier, NCT01780675).

Statistical Analysis

The use of PCI was tabulated and evaluated using χ^2 analyses, controlling for age, gender, TNM stage, year of diagnosis, and socioeconomic status. Multivariable logistic regression was applied to define independent prognostic factors, displayed by odds ratios and 95% confidence intervals (CIs). Significant predictors ($P < .05$) were determined using a backward selection procedure and the likelihood ratio test. Analyses were repeated by TNM stage group, stage I to III, and stage IV. Absolute survival was calculated from the date of diagnosis, and differences in survival between subgroups were evaluated using the log-rank test. The median survival and 5-year survival are reported with the 95% CIs.

Results

The final study series comprised 5165 SCLC patients, 1684 with stage I to III and 3481 with stage IV (Table 1). The median age was

Table 1 Characteristics of Patients Eligible for PCI (n = 5165)

Characteristic	Stage I-III	Stage IV
Age (y)		
18-59	461 (27)	857 (25)
60-69	721 (43)	1384 (40)
70-79	444 (26)	1030 (30)
≥80	58 (3)	210 (6)
Gender		
Male	830 (49)	1979 (57)
Female	854 (51)	1502 (43)
Year		
2009	355 (21)	674 (19)
2010	307 (18)	715 (21)
2011	334 (20)	721 (21)
2012	364 (22)	700 (20)
2013	324 (19)	671 (19)
Socioeconomic status (quintile)		
Highest	299 (18)	660 (19)
High	337 (20)	654 (19)
Intermediate	338 (20)	679 (20)
Low	336 (20)	722 (21)
Lowest	374 (22)	766 (22)
Total	1684	3481

Data presented as n (%).
Abbreviation: PCI = prophylactic cranial irradiation.