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Original Article

Population-based Results of Chemoradiotherapy for Limited Stage Small Cell Lung Cancer in The Netherlands

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Abstract

Aims: Treatment guidelines for limited stage small cell lung cancer (LS-SCLC) favour early concurrent chemoradiotherapy (CRT). Little is known about contemporary, real-world treatment patterns and outcome. We evaluated population-based practice patterns of CRT and corresponding survival in the Netherlands, focusing on the impact of the 2011 national guidelines recommending use of twice-daily (BID) radiotherapy, and treatment outcomes in elderly patients.

Materials and methods: Data for 1635 patients with LS-SCLC treated with CRT from 2010 to 2014 were retrieved from the Netherlands Cancer Registry. The type of CRT was designated as either concurrent BID, concurrent once-daily (OD), concurrent atypical or sequential. Overall survival was the primary end point and prognostic factors were evaluated with multivariable Cox regression and represented by hazard ratios and 95% confidence intervals.

Results: The most common form of CRT used was sequential (41%). The proportion of patients treated BID increased from 13% in 2010–2011 to 36% in 2013–2014 ($P < 0.001$). The median survival was 21 months and did not improve with time ($P = 0.58$). Five year survival was 16% for sequential, 31% for BID (hazard ratio = 0.67, confidence interval 0.57–0.79) and 28% for OD (hazard ratio = 0.73, confidence interval 0.63–0.85). In patients aged 70 years and older, concurrent CRT was less often used than in younger patients (45% versus 66%) and 5 year survival after concurrent CRT was less favourable; 18% versus 32%, respectively.

Conclusions: Outcome data at the population level for LS-SCLC are equivalent to those reported in clinical trials. The increased use of BID schemes since 2011 did not improve survival.

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Keywords: Chemoradiotherapy; concurrent; elderly; patterns of care; small cell lung cancer; survival

Introduction

Small cell lung cancer (SCLC) represents 15% of new lung cancer diagnoses and one-third of the patients present with limited stage disease (LS-SCLC). For fit patients, standard treatment consists of a combination of chemotherapy and radiotherapy, with early concurrent chemoradiotherapy (CRT) as the preferred option above late concurrent CRT and sequential CRT [1]. The ideal radiotherapy dose and

fractionation are still contested. In 1999, the landmark Intergroup 0096 trial reported favourable results for twice-daily (BID) radiotherapy (45 Gy in 30 BID fractions over 3 weeks) compared with once-daily (OD) radiotherapy (45 Gy in 25 OD fractions over 5 weeks) [2]. However, these findings did not lead to a widespread adoption of the BID regimen. Subsequent improvements in disease staging, radiotherapy planning and supportive care may have changed the clinical spectrum since. Two phase III trials were designed to define optimal radiotherapy in the modern era. The European Convert trial started in 2008 and compared BID with an experimental OD regimen of 66 Gy in 33 OD fractions over 6.5 weeks [3]. The North-American

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CALGB 30610 trial also started in 2008 and compares BID with a regimen of 70 Gy in 35 OD fractions over 7 weeks.

Population data suggest that many LS-SCLC patients are ineligible for concurrent treatment due to advanced age or major comorbidity [4]. Concern about the side-effects seems justified, as grade 3–5 toxicity occurred in more than two-thirds of elderly (≥ 75 years) LS-SCLC patients treated with CRT, whereas more than half of such patients received less than four cycles of chemotherapy [5]. However, CRT results in better outcomes than chemotherapy alone, even in the elderly. An observational analysis of elderly (≥ 70 years) patients within the US National Cancer Data Base (NCDB) showed a median overall survival of 15.6 months for patients receiving CRT versus 9.3 months for patients receiving chemotherapy alone [6]. The results for concurrent CRT were marginally better than for sequential CRT, as signified by 3 year survival rates of 24.2% and 20.3%, respectively. Unfortunately, the NCDB is not a population registry, and little is known about the use of dose-fractionation regimens for concurrent CRT in real-world practice. Most general registries do not record technical details, but an NCDB study suggested that radiotherapy treatment duration could be used as a proxy to distinguish OD from BID fractionation [7].

In 2011, the Dutch national guidelines for SCLC were updated and recommended BID over OD, based on the (dated) results of the Intergroup 0096 trial. The present study was initiated to evaluate treatment patterns and population outcomes from 2010 to 2014 and we specifically sought to evaluate the association between age, treatment regimen and survival.

Materials and Methods

Data on patients with primary SCLC diagnosed from 2010 to 2014 were derived from the Netherlands Cancer Registry (NCR), after approval by the NCR Privacy Review Board. In accordance with the regulations of the Central Committee on Research involving Human Subjects, this type of study does not require approval from an ethics committee in the Netherlands. The NCR collects data on all cancer patients diagnosed in the Netherlands, based on notification of newly diagnosed malignancies by the national automated pathological archive and of hospital discharge diagnoses. Information on demographics, diagnosis, staging and treatment is extracted routinely from the medical records by specially trained NCR personnel. Study selection incorporated patients with ICD-O (International Classification of Diseases for Oncology) topography code C34 and morphology codes 8041–8045, excluding patients with a previous diagnosis of lung cancer. Stage information was recorded according to the 7th edition of the TNM Classification of Malignant Tumours from the International Union Against Cancer. Treatment information comprised coding for thoracic radiotherapy, chemotherapy and prophylactic cranial irradiation (PCI). Specifics regarding type of chemotherapy, number of cycles and dose and fractionation of radiotherapy were not available. Doses of chemotherapy and/or

radiotherapy may have been adapted due to toxicity, early progression or palliative intent. Information on treatment response after CRT was not available, as were data about comorbidity or performance status. Information on survival status is updated annually using a computerised link with the national civil registry. For the present analysis, survival information was updated to 1 February 2016. Cause of death information is not available due to privacy regulations.

For patients with TNM stages I–III ($n = 2711$), analyses were restricted to those treated with a combination of chemotherapy and thoracic radiotherapy ($n = 1663$, 61.3%) (Figure 1). Other treatments comprised chemotherapy (18.4%), radiotherapy (3.2%), surgery (4.7%) or best supportive care (12.4%). The actual CRT scheme used was not specifically recorded by the NCR and was inferred by comparing the starting dates of chemotherapy and radiotherapy and the duration of radiotherapy (Table 1). According to Dutch national guidelines, radiotherapy should be started within 30 days of the start of chemotherapy. A BID regimen would require 15 days of radiotherapy, including weekends accumulating to 19–23 days. A OD regimen would require 25–30 days of radiotherapy, including weekends accumulating to 33–43 days. Patients with atypical treatment duration were assembled in a remnant group. Treatment duration of 1–17 days probably reflects partial treatment due to early toxicity and extension of radiotherapy beyond 43 days reflects delay for unknown reasons. The 24–32 bin could not be reliably nominated as BID or OD. Sequential treatment involved the start of radiotherapy more than 30 days after the start of chemotherapy and, hence, also includes some patients with late concurrent treatment. Patients who started radiotherapy before chemotherapy ($n = 23$) or those with missing information on treatment dates ($n = 5$) were excluded from the analysis, leaving a study cohort of 1635 patients. In the Netherlands, 92 hospitals treat patients with lung cancer and radiotherapy is provided by 20 centres. In 2011, national guidelines were revised to recommend use of BID

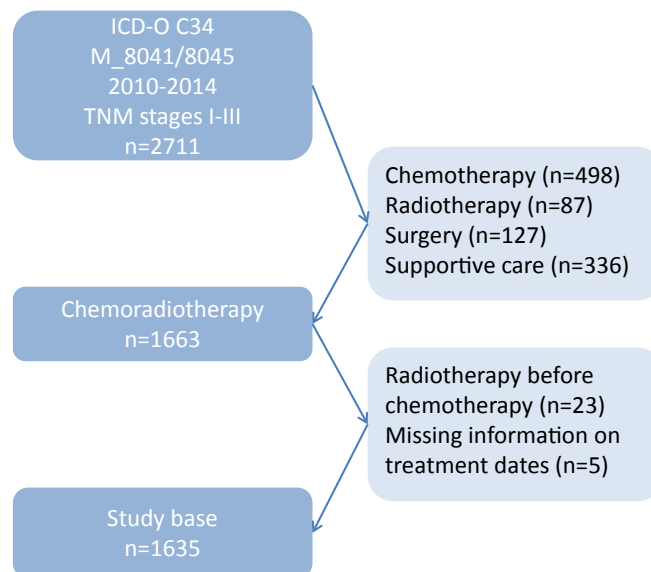


Fig 1. Consort diagram illustrating selection and exclusion criteria.

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