Clinical Oncology 29 (2017) e177–e185

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Treatment Variation of Sequential versus Concurrent Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer Patients in the Netherlands and Belgium

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Received 17 March 2017; received in revised form 28 June 2017; accepted 12 July 2017

Abstract

Aims: Concurrent chemoradiotherapy (CCRT) is considered the standard treatment regimen in non-surgical locally advanced non-small cell lung cancer (NSCLC) patients and sequential chemoradiotherapy (SCRT) is recommended in patients who are unfit to receive CCRT or when the treatment volume is considered too large. In this study, we investigated the proportion of CCRT/SCRT in the Netherlands and Belgium. Furthermore, patient and disease characteristics associated with SCRT were assessed.

Materials and methods: An observational study was carried out with data from three independent national registries: the Belgian Cancer Registry (BCR), the Netherlands Cancer Registry (NCR) and the Dutch Lung Cancer Audit-Radiotherapy (DLCA-R). Differences in patient and disease characteristics between CCRT and SCRT were tested with unpaired *t*-tests (for continuous variables) and with chi-square tests (for categorical variables). A prognostic model was constructed to determine patient and disease parameters predictive for the choice of SCRT.

Results: This study included 350 patients from the BCR, 780 patients from the NCR and 428 patients from the DLCA-R. More than half of the stage III NSCLC patients in the Netherlands (55%) and in Belgium more than a third (35%) were treated with CCRT. In both the Dutch and Belgian population, higher age and more advanced N-stage were significantly associated with SCRT. Performance score, pulmonary function, comorbidities and tumour volume were not associated with SCRT.

Conclusion: In this observational population-based study, a large treatment variation in non-surgical stage III NSCLC patients was observed between and within the Netherlands and Belgium. Higher age and N-stage were significantly associated with the choice for SCRT.

Key words: Concurrent chemoradiotherapy; non-small cell lung cancer; observational study; sequential chemoradiotherapy

Introduction

Lung cancer is a major cause of morbidity and mortality in the developed world [1]. Non-small cell lung cancer (NSCLC) accounts for about 85% of the cases and of those, one third presents with stage III NSCLC, due to invasion of local structures and/or lymph node metastases [2,3].

In randomised clinical trials (RCTs) of inoperable patients with stage III NSCLC, concurrent chemoradiotherapy (CCRT) has proven to be superior in terms of overall survival compared with sequential chemoradiotherapy (SCRT), producing an absolute overall survival benefit of 5.7% and 4.5% in 3 and 5 years, respectively [4]. This benefit is

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http://dx.doi.org/10.1016/j.clon.2017.07.012
0936-6555/

probably the result of improved locoregional control [4–6]. Therefore, CCRT is considered the standard treatment regimen for inoperable patients in both the Dutch and Belgian guidelines. SCRT is proposed for patients who are considered unfit to receive CCRT or when the volume to be irradiated (gross target volume; GTV) is considered too large [7]. As these selection criteria are not very explicit, the 'personalised' choice for either CCRT or SCRT is mainly dependent on the multidisciplinary judgement of the clinical team. As CCRT is associated with a higher risk of toxicity, this treatment is usually given to relatively 'healthier' patients who are generally younger, with little or no comorbidities and a good performance status [8]. Conversely, stage III NSCLC patients are typically elderly with comorbidities, a group poorly represented in clinical trials, which may influence the choice for CCRT. Moreover, CCRT treatment usually requires a well-managed multidisciplinary infrastructure, which may be difficult to deliver in certain hospitals without a radiotherapy facility [9]. Consequently, this may result in a variation of treatment policies across hospitals. A number of studies [6,9–14] previously reported that there is a considerable treatment variation across different hospitals, but it is currently unknown which patient and disease characteristics determine the treating clinical teams' recommendation of CCRT versus SCRT.

This study reports an observational study of the proportion of patients with inoperable stage III NSCLC and who are eligible for CRT actually receiving SCRT. Furthermore, we explored patient, hospital and disease characteristics associated with SCRT compared with CCRT.

Materials and Methods

An observational study was carried out with data from three independent national registries: the Belgian Cancer Registry (BCR), the Netherlands Cancer Registry (NCR) and the Dutch Lung Cancer Audit-Radiotherapy (DLCA-R).

Belgian Cancer Registry

The population-based BCR, covering the full nation, was founded in 2005 and registers patient and tumour characteristics (e.g. gender, age at diagnosis, topography, histology, tumour side, clinical and pathological TNM-stage) of all cancer incidences in Belgium, since 2004 onwards [15,16]. Oncological care programmes from the hospitals and anatomopathological laboratories are legally obliged to report this information to the BCR.

Information about cancer treatment is derived from administrative data obtained from the Belgian health insurance companies (compulsory health insurance system). These data contain information on the reimbursed (cancer-related) diagnostic and therapeutic procedures and pharmaceuticals. Because the administrative health insurance data do not directly refer to a specific diagnosis and often use non-specific nomenclature, timeframes around the date of diagnosis are used to define relevant treatments for specific cancer types.

Reimbursement for radiotherapy treatment planning computed tomography scan was used to identify cases receiving radiotherapy. Cases without a documented radiotherapy start date (about 30%) were assigned the date of their planning computed tomography scan.

Netherlands Cancer Registry

The nationwide NCR is based on notification by pathology departments and hospital discharge records. Population-based coverage was achieved in 1989. Trained data clerks collect information on patient, tumour and treatment characteristics directly from the medical records. Survival status is retrieved from automated linkage with the national civil registry. Only the initial treatment is recorded, excluding treatment related to disease progression. Radiotherapy is coded for irradiation of the primary tumour, excluding radiation of intervention sites or distant metastases [17]. Chemotherapy information (given/not given) is recorded but information on the type of chemotherapy is unavailable.

Dutch Lung Cancer Audit-Radiotherapy

The DLCA-R is a disease-specific national audit that started in 2014. The Dutch Society for Radiotherapy and Oncology aims to ensure transparency regarding clinical outcome, quality and safety of lung cancer treatments in radiotherapy departments throughout the Netherlands. Auditing is considered the best instrument to achieve this. The quality of the radiotherapy treatment becomes apparent using objective and reliable data from accurate registration of clinical outcomes linked to patient and treatment characteristics. The results of the audit provide the local health professionals with a robust instrument to compare and improve their lung cancer treatments.

Quality indicators were defined within the platform of Dutch radiation oncologists and a prospective database was installed in October 2012. Patients receiving primary thoracic radiation treatment with curative intent for (primary or recurrent) stage I–IIIB lung cancer from January to December 2014 were included in the registry. Information on patient, tumour and treatment characteristics, pulmonary function (FEV1, DLCO and VO2 max), the incidence and severity of acute toxicity, mortality within 3 months of radical radiotherapy and the time interval between diagnostic work-up and the start of radiotherapy was collected. Hence, the DLCA-R provides supplementary information on determinants that were not measured within the BCR and NCR [18].

For practical reasons, several of the radiotherapy departments did not fully participate in 2014. In order to avoid chance findings, radiotherapy departments ($n = 13$) that included less than five patients with stage III NSCLC were excluded from the analyses. Consequently, the current study