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Patterns of treatment and survival among older patients with stage III non-small cell lung cancer

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ABSTRACT

Introduction: Patterns of treatment and survival are largely unknown for older patients with stage III non-small cell lung cancer (NSCLC) in daily clinical practice.

Methods: All patients ≥65 years with stage III NSCLC (2009–2013) were included from the population-based Netherlands Cancer Registry. Descriptive and multivariable treatment and survival analyses were stratified for patients aged 65–74 years and ≥75 years.

Results: Compared to older patients (n = 3163), those aged 65–74 years (n = 3876) underwent more often surgery (21% vs 12% for stage IIIA), chemoradiotherapy (47% vs 22% for both stage IIIA and IIIB), and chemotherapy (23% vs 12% for stage IIIB), and received less radiotherapy (8% vs 22% for both stage IIIA and IIIB). One-year survival was significantly higher among patients aged 65–74 compared to those aged ≥75 (61% vs 43%, for stage IIIA and 45% vs 30% for stage IIIB; P < .01). However, stratification of treatment showed similar survival rates between age groups. Among patients aged 65–74 years, the multivariably adjusted hazard ratio (HR) of death was twice as high for patients receiving radiotherapy (HR 1.9 (95%CI 1.6–2.2) for stage IIIA and HR 2.5 (95%CI 2.1–3.0) for stage IIIB) and chemotherapy (HR 2.2 (95%CI 1.9–2.5) and HR 2.2 (95%CI 1.8–2.7), respectively) compared to chemoradiotherapy, and were slightly lower for patients aged ≥75 years receiving radiotherapy (HR 1.6 (95%CI 1.4–1.9) and HR 1.8 (95%CI 1.5–2.1), respectively) and chemotherapy (HR 2.2 (95%CI 1.8–2.7) and HR 1.8 (95%CI 1.5–2.2), respectively). Comorbidity was not significantly associated with poorer survival (p = .07).

Conclusion: Chemoradiotherapy was more often applied among patients aged 65–74 years compared to those aged ≥75. While survival was worse for patients aged ≥75 years, differences between age groups largely disappeared after stratification for treatment. Future research should focus on predictive patient characteristics to distinguish patients within the heterogeneous older population who can benefit from curative-intent treatment.

1. Introduction

Half of patients with non-small cell lung cancer (NSCLC) are aged 65 years or older at the time of diagnosis, whereas one in four is aged 75 years or older in the Netherlands [1]. Overall 5-year survival remains below 15% for patients with stage III NSCLC in daily clinical practice [2]. Concurrent chemoradiotherapy is considered standard treatment for patients with unresectable stage III NSCLC, as it results in a survival benefit of 5,7% at 3 years and 4,5% at 5 years compared to sequential chemoradiotherapy according to clinical trials [3–5]. In case

Abbreviations: BSC, Best Supportive Care; HR, hazard ratio; ICD-O, International Classification of Disease for Oncology; NSCL, Cnon-small cell lung cancer; OS, overall survival; TKI, Tyrosine Kinase Inhibitor; TNM, tumour node metastasis; 95%CI, 95% confidence interval

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of resectable stage IIIA NSCLC, surgery with adjuvant chemotherapy is considered standard treatment [3–5],[3–5]. Older and frail patients are often excluded from clinical trials as strict eligibility criteria such as performance status, age, and strict levels of organ function are retained in order to minimize the risk of complications [6]. Elderly patients with NSCLC receive standard treatment less often [7–9]. This could be explained by a lack of evidence to extrapolate treatment guidelines to older and vulnerable patients in everyday clinical practice. Despite this lack of evidence, modest increases in the application of chemoradiotherapy were seen for older patients over time in the Netherlands [2]. A recent retrospective study from our group indicated that survival among patients with unresectable stage III NSCLC ≥70 years in the southeastern part of the Netherlands was not significantly superior for those who received concurrent chemoradiotherapy as compared to sequential chemoradiotherapy and even radiotherapy alone. Also, severe comorbidity was associated with worse treatment tolerance and worse survival in case of concurrent and sequential chemoradiotherapy [10]. Therefore, it is important to assess patterns of treatment and survival in this heterogenous and older population in order to distinguish patient groups for optimal treatment strategies by patient and tumour characteristics.

The aim of this population-based study was to describe unselected patients with stage III NSCLC aged 65–74 years and those aged ≥75 years regarding patterns of treatment and survival in relation with patient and tumour characteristics in the Netherlands.

2. Methods

All patients diagnosed with stage III NSCLC during 2009–2013 who were aged 65 years or older were retrieved from the population-based Netherlands Cancer Registry. Patients diagnosed by autopsy were not included. Since 1989, trained registrars routinely collect data from medical records regarding patient and tumour characteristics of all newly diagnosed cancer patients in the Netherlands. These data are > 95% complete and have national coverage. Vital status was retrieved from the nationwide population registries network (follow-up until February 1st 2017). This study was approved by the Privacy Review Board of the Netherlands Cancer Registry. The Central Committee on Research involving Human Subjects (CCMO) judged that approval from an ethics committee was not required.

The International Classification of Disease for Oncology (ICD-O3) [11,12] was used to code topography (C34) and morphology (invasive 8010–8020, 8022–8035, 8046–8230, 8243–8246, 8250–8576, 8972, 8980–8982, and 9110) [13]. Diagnoses of other histologies or no pathological verfication were excluded (Fig. 1). Stage of disease was classified according to pathological Tumor Node Metastases (TNM) supplemented with clinical TNM (edition 6 up to 2009, edition 7 from 2010 onwards) [14]. The patient population was described according to two age groups (65–74 years and ≥75 years). Gender, histology (adenocarcinoma, squamous cell carcinoma, large cell carcinoma and other NSCLC[13]), and stage (IIIA and IIIB) were included in analyses. Information on comorbidity was available for patients in the southeastern part of the Netherlands only, covering approximately 15% of the Dutch population. Comorbidity was registered according to a slightly adapted version of the Charlson Comorbidity score [15]: it was classified as number of comorbid conditions (0, 1, or ≥2), and type of comorbidity (respiratory, cardiovascular, hypertension, diabetes, previous malignancy, digestive or CVA/hemiplegia). Obtained primary treatment was categorized as surgery (including (neo)adjuvant therapy (if applicable) for stage IIIA), chemoradiotherapy (including radiotherapy with sensitizer, chemotherapy followed by radiotherapy), radiotherapy alone (both curative-intent and palliative), chemotherapy alone, and Best Supportive Care (BSC). When the time interval between treatments was available, concurrent chemoradiotherapy (< 30 days between dates of start of both chemotherapy and radiotherapy) and sequential chemoradiotherapy (> 30 days between chemotherapy and radiotherapy) could be distinguished. However, time between treatments was unspecified in 22% of patients receiving chemoradiotherapy. Subanalyses were not performed for concurrent and sequential chemoradiotherapy as a large proportion of those receiving chemoradiotherapy could not be categorized. Overall survival (OS) was calculated from the time of diagnosis until death or until February 1st 2017, including median, 1-year, and 3-year OS rate.

2.1. Statistical analyses

All analyses were performed using IBM SPSS Statistics 22.0. Stratification according to stage was consistently applied as available treatment options and prognoses differ for those with stage IIIA and IIIB NSCLC. Patient and tumour characteristics were described according to age groups, and statistical significant differences ($P < 0.05$ two sided) were determined by the X^2-test for categorical variables and the Mann-whitney *U* test for medians of continuous variables. OS rates were calculated for each age group, stage, and obtained treatment. OS was depicted by estimates of the Kaplan-Meier method and significant differences between treatment groups were determined by the log-rank

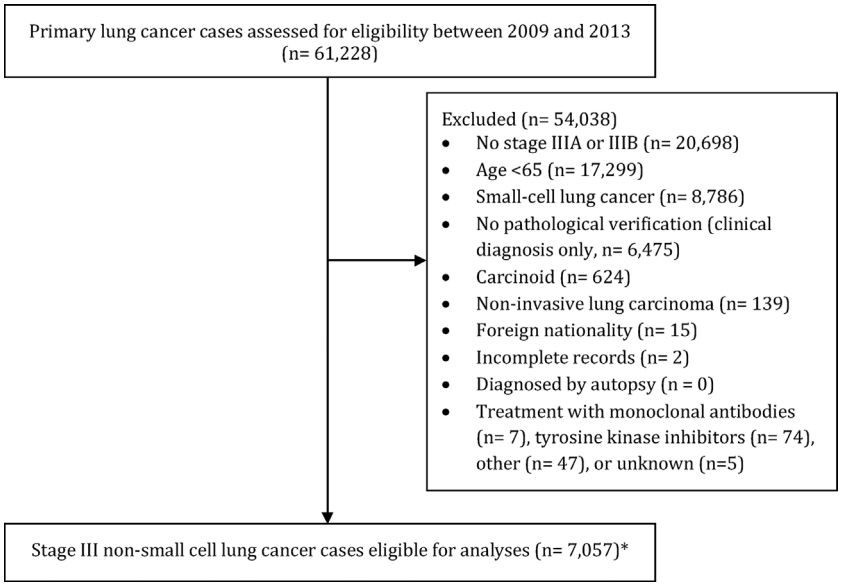

Fig. 1. Flow chart of eligible older patients diagnosed with stage III non-small cell lung cancer (2009–2013).
*This number can slightly deviate from the finally included number of cases as some cases could be added or excluded from the database after initial data retrieval for this study