Early-stage lung cancer in elderly patients: 
A population-based study of changes in treatment patterns and survival in the Netherlands

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Background: Elderly patients with stage I non-small-cell lung cancer are less likely to undergo curative treatment. However, the introduction of new treatment options such as stereotactic ablative radiotherapy (SABR) may improve treatment rates. We evaluated time trends in treatment patterns and survival in the entire Netherlands population for patients diagnosed between 2001 and 2009.

Patients and methods: Details of 4605 elderly Dutch patients were obtained from the Netherlands Cancer Registry, containing data on all cancer patients in a population of 16 million. Three consecutive time periods were studied: 2001–2003 (A, before SABR became available), 2004–2006 (B, increasing availability), and 2007–2009 (C, full availability).

Results: Between period A and C, there was a 7% absolute reduction in patients going untreated, corresponding to an 8-month improvement in median survival (P < 0.001). Radiotherapy utilization increased from 31% to 38%, whereas surgical utilization remained constant (37%). Significant improvements in survival were observed in the radiotherapy subgroup (P < 0.001) and surgery subgroup (P < 0.001), not in patients going untreated. There was no evidence of stage migration.

Conclusions: Population-based increases in survival of elderly stage I lung cancer patients were seen between 2001 and 2009. The introduction of SABR correlated with a decline in the number of untreated patients.

Key words: elderly, epidemiology, lung cancer, SABR, SBRT, stereotactic radiotherapy

Introduction

Lung cancer is the most common cause of cancer death worldwide [1]. Improvements in overall survival in recent decades have been minimal: 5-year relative survival for non-small-cell lung cancer (NSCLC) was 13% in 1975–1977, increasing to 16% by 1999–2005 [2]. If untreated, the 5-year overall survival in stage I NSCLC is ~14% [3]. Treatment patterns can vary significantly across geographic regions, with major differences observed between patients in the United States and Europe [4, 5]. Five-year survival for lung cancer can vary nearly twofold between countries in Western Europe; these differences in survival are observed mainly within the initial months after diagnosis and are likely due to variations in diagnostic practice or treatment [4].

Surgery is considered the treatment of choice in fit patients with early-stage NSCLC [6]. However, <50% of such patients aged older than 75 years undergo surgery [5], for reasons including comorbidity that increases operative risks, frailty, personal choice, or a perceived lack in treatment benefit. The use of surgery in elderly patients can potentially be improved by the introduction of less invasive surgical techniques such as video-assisted thoracoscopic surgery (VATS). For patients who are considered unfit for open or VATS lobectomy, radiotherapy is an alternative treatment with curative intent. Although conventional radiotherapy was associated with modest improvements in survival compared with no treatment [7], the advent of stereotactic ablative radiotherapy (SABR) has been associated with further improved survival [8]. SABR is a form of high-precision radiotherapy that is characterized by the use of high biological doses of radiation and delivered in a few fractions as an outpatient procedure [9, 10]. Local control rates of >90% have been reported with SABR [11, 12], with limited toxicity seen even in frail elderly patients [13].

Population-based analyses are useful in studying the effects of introducing new treatments [14]. A previous smaller analysis of regional data from the North Holland population registry revealed a significant reduction in the number of untreated elderly patients with stage I NSCLC, which followed the introduction of SABR, as well as an increase in median survival.
of all patients undergoing radiotherapy [15]. However, all SABR treatments in this regional analysis were performed in two national referral centers, raising the question as to whether outcomes from specialized radiotherapy centers will be reproducible nationally. Other Dutch centers increasingly adopted SABR since 2006, and the aim of our study was to evaluate treatment utilization and survival in elderly patients with a stage I lung cancer for the entire Dutch population.

**methods and materials**

**data source and study population**
The Netherlands Cancer Registry (NCR) collects individual data on all cancer cases from all 92 Dutch hospitals, in a total population of 16 million people. The 92 hospitals include eight academic hospitals and one specialized oncology center; 74 centers provided lung cancer surgery and 21 provided radiotherapy. The NCR has complete survival data as it is electronically linked with Dutch civil population records of all births and deaths in the Netherlands. Data including patient and treatment characteristics are collected from individual patient records by specially trained data managers. Patients were classified using the International Union Against Cancer Tumor Node Metastasis classification version 6. Specific staging procedures, performance scores, and comorbidities are not recorded. The details of surgery performed are recorded, but specific radiotherapy details such as dose or fractionation are not. Follow-up was complete until 1 February 2011. We obtained data from the NCR on patients aged 75 years and older, who were treated between 2001 and the end of 2009.

In the Netherlands, SABR became available at a Dutch academic hospital in 2003, and its use became widespread in all Dutch provinces after 2007. Data were analyzed for three periods: period A (from 2001 to 2003), which preceded the introduction of SABR, period B (2004–2006), a transition period in which SABR became available in three other centers nationwide, and period C (2007–2009), when SABR became available in all Dutch provinces. Statistical comparisons were performed between period A and period C. All Dutch radiotherapy centers providing SABR were individually contacted to determine the number of radiotherapy patients receiving SABR in each of the three time periods. Based on available data, we estimated the use of SABR in patients who underwent radiotherapy group in period C was >75% [15].

**statistical analysis**
Statistical analysis was performed using STATA (version 10, StataCorp LP, College Station, TX). Baseline differences in treatment groups (radiotherapy, surgery, or neither) and treatment eras were compared using t-tests for continuous variables and Chi-square tests for categorical variables as appropriate. Overall survival differences were determined using Kaplan–Meier curves and log-rank tests (period A versus period C). A Cox regression analysis was performed to analyze factors determining overall survival, with all potential confounders available in the NCR included into the model. All statistical tests were two sided, with a threshold of \( P \leq 0.05 \) indicative of statistical significance.

**results**

**patient groups**
Between 2001 and end of 2009, the number of residents in the Netherlands aged 75 years or older increased from 720,000 to 1.14 million, and a total of 4605 patients developed a stage I lung cancer. Primary treatment modality was surgery in 1698 (36.9%) patients, radiotherapy in 1570 (34.1%) patients, whereas no curative treatment was performed in 1337 (29.0%) patients. An analysis of all patients diagnosed with lung cancer in the Netherlands revealed that the percentage of cases of stage I disease remained constant in all periods (20%), suggesting that no stage migration occurred for these patients (supplemental Table S1, available at Annals of Oncology online).

Patient and treatment characteristics are shown in supplemental Table S2 (available at Annals of Oncology online). On average, surgical patients were younger and had earlier stage tumors than patients in the other two groups. Median follow-up was 55 months for the whole group (100, 63, and 32 months for periods A, B, and C, respectively).

In patients undergoing surgery, 69% (1174) underwent a lobectomy, 10% (168) pneumonectomy, 8% (127) bilobectomy, 6% (104) sublobar excision, 1% (16) sleeve lobectomy, and the procedure was unknown in 6% (109). Following surgery, the T-stage was upgraded from cT1-2 to pT3-4 in 7.7% of patients. Similarly, the N-stage was upgraded from cN0 to pN1 in 6.6% and to pN2 in 3.4% for T1 tumors; for T2 tumors, N-stage was upgraded from cN0 to pN1 in 18.9% and to pN2 in 7.6%.

Significant changes in treatment patterns were observed across time periods (Chi-square \( P < 0.001 \); supplemental Figure S1, available at Annals of Oncology online). The number of patients not undergoing curative-intent treatment decreased from 31.9% to 24.9%, and this corresponded with an increase in patients receiving radiotherapy from 31.2% to 37.7%. Surgical utilization rates remained constant at 37%.

**overall survival**
The 30- and 90-day mortality rates after surgery were 5.4% and 9.3%, respectively. The 30-day surgical mortality rates decreased from 6.4% to 3.9% between periods A and C, and the corresponding 90-day mortality decreased from 11.5% to 7.0%. Although the true 30- and 90-day mortality rates after radiotherapy could not be derived because the start date of radiotherapy was not available in the database, those rates measured from the date of diagnosis were 0.6% and 3.3% for the radiotherapy group, respectively. The 30- and 90-day mortality rates measured from the date of diagnosis for the no-treatment group were 17.9% and 33.3%, respectively.

The median overall survival of all patients was 19.6 months. Kaplan–Meier survival estimates by time period for the whole group, and for each treatment subgroup, are shown in Figure 1A–D, with results of the multivariable analysis shown in supplemental Table S3 (available at Annals of Oncology online). Patients treated in period C had a significant improvements in survival [hazard ratio (HR) 0.72; 95% confidence interval (CI) 0.66–0.79] compared with those treated in period A, with median survival increasing from 16.4 to 24.4 months (\( P < 0.001 \)). The largest reduction of the HR of death was seen in the radiotherapy group (HR 0.64, 95% CI 0.56–0.74), where median survival increased from 16.8 to 26.1 months (\( P < 0.001 \)). Similarly, a significant reduction in the HR of death was also seen in the surgical group (HR 0.79, 95% CI 0.66–0.94), and no significant differences were observed in the no-treatment group (HR 0.90, 95% CI 0.78–1.04). Two-year
survival in the radiotherapy group improved from 35.8% to 52.5% and that for patients treated with surgery from 61.3% to 69.6%.

Since pathological proof of malignancy was unavailable in many patients in the radiotherapy and no-treatment groups, as a sensitivity analysis, the survival analysis was repeated including only patients with pathological proof of malignancy in those subgroups, and the results were similar (radiotherapy group shown in supplemental Figure S2, available at Annals of Oncology online).

discussion

This population-based study demonstrates a significant increase in the proportion of elderly patients with a stage I NSCLC receiving curative-intent therapy in the entire Netherlands between 2001 and 2009. The median survival of all 4605 patients increased by 8 months, and survival improvements were seen in patients undergoing both radiotherapy and surgery, in the absence of stage migration. The median survival in untreated patients was unchanged at ∼6.6 months, a figure similar to the 7 months reported in an Surveillance, Epidemiology and End Results analysis for the period 1992–2002 [7].

Although the gold standard for assessing clinical benefit of a new treatment approach such as SABR is the randomized controlled phase III trial [16], such data are not available to compare SABR against older radiotherapy techniques to definitely prove a survival benefit. SABR has nevertheless become widely accepted in the Netherlands as a result of data from prospective multicenter studies in the United States and Scandinavia [11, 12] and large single-center reports showing good tolerance and local control using short SABR schedules [13, 17]. Phase III data to answer this question may never become available for several reasons: elderly patients with cancer participate less frequently in clinical trials [18] and randomized studies can be difficult in evaluating new technologies, due to lack of individual or collective equipoise, the long time frame required for randomized, controlled trials in combination with a rapid implementation of new technologies, and the difficulty in measuring small changes in clinical outcomes due to stepwise improvements in quality of treatment delivery [16]. Furthermore, based on retrospective results, SABR has already been widely recognized to be superior to conventional radiotherapy and has been accepted in national guidelines [8, 19].

Overall survival in our study also improved in patients undergoing surgery. Both the 30- and 90-day postoperative
mortality rates improved during the study period, a finding which might be explained by improved perioperative care, use of less extensive surgical resections, and a trend to growing centralization of thoracic surgery in higher volume hospitals. Although the 90-day mortality of 7% is higher that has been reported in recent clinical trials [20], much larger population-based analyses have revealed 30-day survivals of 6.9% in elderly subgroups [21]. Further improvements in surgical outcomes may be expected in coming years due to the move toward a greater centralization of thoracic surgery and increased use of VATS procedures in the Netherlands [22].

The constant proportion of patients with a diagnosis in stage I NSCLC suggests that no stage migration has taken place in our population, even though 2-[fluorine-18]fluoro-2-deoxy-D-glucose positron emission tomography (PET) may not have been used to stage every patient during the initial period of study. This finding is consistent with data showing that PET imaging detects occult distant metastases in only 3%–5% patients with a clinical stage I [23]. Similarly, computed tomography screening for lung cancer was not routinely performed in the Netherlands outside the randomized NELSON screening trial, which was conducted from April 2004 through December 2006 [24]. Screening was performed in patients aged between 50 and 75 years, and the mean (±standard deviation) age of the screened participants was 59 ± 6 years. The low number of detected early-stage lung cancers (54 patients) of any age in the NELSON study in the second round, combined with the small chance of overlap of study populations, suggests that the effect of screening on survival improvements in our study population was negligible.

The survival improvements observed in our radiotherapy cohort are reassuring as dissemination of complex radiotherapy techniques have been previously shown to result in large variations in planning and treatment delivery, all of which can obscure improved outcomes [25]. The widespread implementation of SABR in the Netherlands was preceded by adoption of national technical guidelines for delivery and imaging [26, 27].

The data presented herein also indicate a need for improved staging in some subgroups of patients. In operated clinical T2N0 tumors, e.g. pathological ipsilateral nodal metastases were found in 18.9% of patients, with occult mediastinal nodal metastases in 7.6%. This indicates a need for improved pre-treatment staging, such as using endoscopic ultrasound-guided biopsy for such patients [28]. Pathological proof of malignancy was not obtained in 28% of Dutch patients in the radiotherapy group, a figure similar to that reported for Scandinavian patients [11]. Previous prospective surgical clinical trials in the Dutch population [29, 30], as well as a single institution Dutch study [31], revealed that the likelihood of a benign diagnosis with such a presentation in the Netherlands is <5%. A sensitivity analysis in the present study showed that the current results were similar when patients without pathological proof of malignancy are excluded from analysis.

The results of this study should be considered in the context of its strengths and limitations. The large sample size and population-based design allows for robust statistical analyses with conclusions that are inherently generalizable to the Dutch population. However, like in most population-based studies, not all preferred, individual-level patient data are available, such as comorbidities, performance status, cause of death, and quality of life outcomes. We also cannot rule out the presence of other unidentified confounders that could have had an impact on the time trends detected here; however, other changes in treatment or supportive care would be unlikely to have such a profound impact on survival in this population of elderly patients with stage I lung cancer.

Our study does not examine the cost-effectiveness or cost utility of SABR, which is a crucial question in an era of dwindling health care funding, and is essential to help guide healthcare jurisdictions in the implementation of SABR. Preliminary data suggest that SABR is the most cost-effective treatment for medically inoperable early-stage NSCLC [32, 33], but such findings may vary in different international settings.

In conclusion, this population-based study shows that the implementation of SABR in the Netherlands is associated with a decrease in the proportion of patients left untreated, and an improvement in overall survival was seen during the study period in both the surgical and the radiotherapy group. This provides high-level supporting evidence for the benefits of modern surgery and SABR for the treatment of elderly patients with stage I lung cancer instead of a wait-and-see policy.

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