Clinical Staging of Stage I Non-Small Cell Lung Cancer in the Netherlands—Need for Improvement in an Era With Expanding Nonsurgical Treatment Options: Data From the Dutch Lung Surgery Audit

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Background. **The clinical stage of non-small cell lung cancer (NSCLC) determines the initial treatment, whereas the pathologic stage best determines prognosis and the need for adjuvant treatment. In an era in which stereotactic ablative radiotherapy (SABR) has become an alternative modality to surgical intervention, clinical staging is even more important, because pathologic staging is omitted in the case of SABR. The objective of this study was to determine the concordance between clinical and pathologic stage in routine clinical practice for patients with early-stage NSCLC.**

Methods. **Prospective data were derived from the Dutch Lung Surgery Audit (DLSA) in 2013 and 2014. Patients with clinical stage I NSCLC who underwent surgical resection and had a positron emission tomography-computed tomography (PET-CT) scan in their clinical workup were selected. Clinical and pathologic TNM (cTNM and pTNM) stages were compared.**

Results. **From a total of 1,790 patients with clinical stage I, 1,555 (87%) patients were included in this analysis. Concordance between cTNM and pTNM was 59.9%. Of the patients with clinical stage I, 22.6% were upstaged to pathologic stage II or higher. In total, 14.9% of all patients with clinical stage I had nodal metastases, and 5.5% of all patients had unforeseen N2 disease. In patients with clinical stage T2a tumors, 21.3% had nodal metastases, 14.5% being N1 and 6.7% being N2 disease.**

Conclusions. **Concordance between clinical and pathologic stage is 59.9%. In patients with clinical stage I NSCLC, 22.6% were upstaged to pathologic stage II or higher, which is an indication for adjuvant chemotherapy. Improvement in accuracy of staging is thus needed, particularly for these patients.**

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Survival of patients with stage I non-small cell lung cancer (NSCLC) remains disappointing, with 5-year survival rates after anatomical surgical resection ranging from 60% to 80% [1]. Staging lung cancer is very difficult, with low accuracy of the staging process [2–5]. The concordance between clinical and pathologic staging in early-stage lung cancer is between 65% and 75%. Most studies on this subject were published in the era before positron emission tomography-computed tomography (PET-CT) [4–7]. When understaging a patient with early-stage NSCLC, undertreatment is likely, which might negatively impact survival. In the Netherlands, according to the national evidence-based guideline, the staging algorithm of stage I NSCLC is composed of PET-CT, and in the case of an abnormal PET scan or an enlarged mediastinal node (short-axis diameter >1 cm), invasive diagnostic procedures and histopathologic proof are recommended using endoscopic ultrasonography/endobronchial ultrasonography (EUS/EBUS). If these examinations prove normal, a mediastinoscopy is indicated. Invasive staging of the mediastinum is also recommended in patients with a central tumor or N1 lymph node involvement. Pathologic proof of the primary tumor is not mandatory preoperatively [8].

The Dutch Lung Surgery Audit (DLSA) is a nationwide prospective database that is used to monitor the staging process in patients who undergo surgical procedures for

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Abbreviations and Acronyms

CI = confidence interval
CT = computed tomography
cTNM = clinical TNM
D_{LCO} = diffusion capacity of the lung for carbon monoxide
DLSA = Dutch Lung Surgery Audit
EBUS = endobronchial ultrasonography
ECOG = Eastern Cooperative Oncology Group
EUS = endoscopic ultrasonography
FEV_1 = forced expiratory volume in 1 second
NSCLC = non-small cell lung cancer
OR = odds ratio
PET-CT = positron emission tomography-computed tomography
pTNM = pathologic TNM
SABR = stereotactic ablative radiotherapy
VATS = video-assisted thoracoscopy

early-stage NSCLC. The advantage of such population-based data is that they represent daily practice, rather than selected populations in expert centers.

As clinical staging remains a challenge, so does the treatment of early-stage lung cancer. Surgical intervention and stereotactic ablative radiotherapy (SABR) are effective treatments with different morbidities and potential mortality. Initially SABR was used as a treatment modality for patients unfit for operative treatment [9, 10]. Because of excellent results in locoregional control, which have been proved in retrospective and phase II prospective studies, SABR is becoming an alternative treatment used more and more for patients who are also candidates to undergo operative treatment [11–16].

Recently Chang and colleagues [17] pooled data from 2 prematurely finished randomized trials to conclude that SABR is a good alternative to surgical treatment in patients with stage I NSCLC regarding overall survival, recurrence-free survival at 3 years, local recurrence, regional recurrence, distant metastasis, and complications. Although these are the only randomized controlled data on this subject, the robustness of the conclusions was strongly challenged. One of the criticisms of the study concerned the lack of final pathologic staging in patients treated with SABR [18–22]. One of the major problems in the absence of surgical staging is the presence of lymph nodes with metastases, with reported rates of 11.7% and almost 5% to 10% being unforeseen pathologic N2 nodes [7, 23]. In the case of SABR, such nodes would not receive a therapeutic dose of radiation nor would the patients receive adjuvant chemotherapy.

In an era in which the indication for SABR is being extended with only minimal prospective randomized data available, we aimed to investigate the concordance between clinical (c)TNM and pathologic (p)TNM in early-stage lung cancer, especially with regard to lymph node staging. This article is an in-depth analysis of the stage I cohort from a total study population described elsewhere, given the importance of accurate staging, particularly in patients with stage I disease, because alternative nonsurgical treatment modalities are now available in which there is no definitive pathologic review of the malignancy.

Patients and Methods

Data Source

In the Netherlands, the DLSA started in 2012 as a national prospective clinical database. The objective of this database was to register the care process and the outcome of all patients in routine practice undergoing operative treatment for benign and malignant lung tumors. In 2013 and 2014, 41 of 48 (85%) Dutch hospitals performing operations on patients with lung cancer participated, and 85% of patients undergoing lobectomy because of lung cancer were registered in this database. We used this database to compare cTNM and pTNM in early-stage lung cancer. The clinical stage is defined in the DLSA as the last known stage before resection—after PET-CT, EUS/EBUS, or mediastinoscopy, or a combination of these modalities. Because these data are collected as part of everyday routine clinical practice, no informed consent was mandatory.

Patients

All patients with clinical stage I NSCLC who underwent an anatomical parenchymal resection (pneumonectomy, lobectomy/bilobectomy, or sublobar resection) between January 1, 2013 and December 31, 2014 and who were registered in the DLSA were evaluated. According to the seventh edition of *TNM: Classification of Malignant Tumours* [24], this is T1a/T1b/T2a disease, meaning a tumor size up to 5 cm, no lymph node invasion, or any size less than 5 cm with invasion of the main stem bronchus but growth greater than 2 cm distal from the carina, or infiltration into the visceral pleura. Disease is also classified as cN0 if nodes/stations are enlarged or show fluorine 18-fluorodeoxyglucose uptake, and those nodes/stations were further evaluated and found to be normal before operation using EUS/EBUS/mediastinoscopy. Minimal data requirements for inclusion in the analysis were information on cTNM and pTNM stages, type of parenchymal resection, and postoperative histopathologic results. Patients who had acute symptoms, a histopathologic type other than NSCLC, neoadjuvant treatment, or no available PET-CT scans were excluded.

Outcome

The primary outcome is discrepancy (understaging or overstaging) between cTNM and pTNM stages for the different clinical stages. Secondary outcomes are the patients misdiagnosed based on nodal and tumor stage and the number of patients who should receive adjuvant therapy based on the pathologic outcome. An analysis on accuracy of staging by histologic type was also performed.