Lungscape: Resected Non–Small-Cell Lung Cancer Outcome by Clinical and Pathological Parameters

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Introduction: The Lungscape project was designed to address the impact of clinical, pathological, and molecular characteristics on outcome in resected non–small- cell lung cancer (NSCLC).

Materials and Methods: A decentralized biobank with fully annotated tissue samples was established. Selection criteria for participating centers included sufficient number of cases, tissue microarray building capability, and documented ethical approval. Patient selection was based on availability of comprehensive clinical data, radical resection between 2003 and 2009 with adequate follow-up, and adequate quantity and quality of formalin-fixed tissue.

Results: Fifteen centers contributed 2449 cases. The 5-year overall survival (OS) was 69.6% and 63.6% for stages IA and IB, 51.6% and 47.7% for stages IIA and IIB, and 29.0% and 13.0% for stages IIIA and IIIB, respectively ($p < 0.001$). Median and 5-year relapse-free survival (RFS) were 52.8 months and 47.3%, respectively. Distant relapse was recorded for 44.4%, local for 26.0%, and both for 16.9% of patients. Based on multivariate analysis for the OS, RFS, and time to relapse, the factors significantly associated with all of them are performance status and pathological stage.

Conclusion: The aim of this report is to present the results from Lungscape, the first large series reporting on NSCLC surgical outcome measured not only by OS but also by RFS and time to relapse and including multivariate analysis by significant clinical and pathological prognostic parameters. As tissue from all patients is preserved locally and is available for detailed molecular investigations, Lungscape provides an excellent basis to evaluate the influence of molecular parameters on the disease outcome after radical resection, besides providing an overview of the molecular landscape of stage I to III NSCLC.

Key Words: NSCLC, TNM stage, Surgery, Patients' and pathological characteristics, Outcome.

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The seventh edition of the tumor, node, metastasis (TNM) system reliably serves in estimating the prognosis of patients with non–small-cell lung cancer (NSCLC) and provides the basis for decisions on treatment strategies. For operable patients with earlier stages of disease, surgery remains the established standard of care. For patients with a complete resection of pathological stage II and III tumors, adjuvant chemotherapy has been proven to increase the 5-year survival by an absolute 4.0%,[1] whereas a benefit from adjuvant radiotherapy remains uncertain and, if existing, probably is restricted to stage III disease.

The seventh edition of the TNM classification of NSCLC was published in 2009. It is built on the retrospective analysis of patients from 46 sources from more than 20 countries treated by all modalities from 1990 to 2000 to guarantee a 5-year follow-up. The survival analysis was based on 67,725 cases of NSCLC, of which data on pathological stage were available in 16,952 cases.[2]

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¶¶¶For details on ETOP Lungscape Investigators, see Appendix.

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Since the identification of activating mutations in the epidermal growth factor receptor gene as a molecular driver for a subset of NSCLC, it has become recognized that adenocarcinoma of the lung no longer represents a single entity but rather comprises a growing spectrum of distinct molecular subtypes for which specific systemic therapies have entered clinical practice or are currently under investigation.[3] A similar, potentially even more complex picture is emerging in squamous cell lung cancer.[4]

The Lungscape project was designed to address the challenges of studying the molecular epidemiology of lung cancer and to expedite our knowledge of current and evolving clinical and molecular biomarkers. As the basis of this work, a decentralized biobank with fully annotated tissue samples was created to elucidate the outcome of clinically, pathologically, and molecularly characterized subgroups of resected stage I to III NSCLC. Fifteen centers contributed their data on a total of 2449 patients. The aim of this study is to describe the outcome, including overall survival (OS), as reported in the *International Association for the Study of Lung Cancer* database,[2] but also for the first time in a large surgical series, relapse-free survival (RFS) and time to relapse (TTR), according to pathological stage, histology, and clinical parameters for 2449 patients with resected NSCLC.

PATIENTS AND METHODS

Patient Selection and Data Capturing

Data on patients with pathological stage I to III NSCLC in 14 European and one Chinese center have been collected retrospectively, according to the Lungscape protocol. Selection criteria for participating centers included sufficient numbers of cases, availability of a full clinicopathological data set, tissue microarray building capability, and documented ethical approval for investigations on tissue samples and sharing associated clinical data. Patient selection was based on radical surgical resection performed between January 1, 2003, and up to December 31, 2009, allowing for a follow-up of at least 3 years, comprehensiveness of clinical annotation, and adequate formalin-fixed paraffin-embedded tissue.

After data capture in the iBiobank, a central electronic database used to store anonymized comprehensive molecular and clinical data, a systematic medical data review of every case was performed to check for plausibility, to optimize staging accuracy under the seventh TNM classification,[2] and to confirm availability of tissue. To facilitate quality assurance in regard to tissue and pathological staging, upload of the original anonymized pathology reports to the iBiobank database was mandatory. Clinical data were categorized into mandatory parameters necessary for case submission and acceptance by central review, and desirable parameters as listed in Supplementary Table 1 (Supplemental Digital Content, http://links.lww.com/JTO/A687). Tissue tracking was also systematically recorded, allowing verification of biological material availability.

Statistical Analysis

Comparison of patient and tumor characteristics was performed by Fisher's exact and Mann-Whitney tests for categorical and continuous variables, respectively. Adjustment for multiple testing was not used. All tests performed were two-sided. Statistical analysis was performed in SAS version 9.3.

Log-rank tests and Cox model Wald tests were used for comparisons of time-to-event end points between subgroups of interest. The outcome is measured by three time-to-event end points: OS, RFS, and TTR. OS is defined as time from surgery until death. RFS is defined as time from surgery until documented relapse or death from any cause. To avoid competing risks of death and better define the surgical outcome, the end point of TTR is used. TTR is defined as the time from surgery until documented relapse or death due to the disease. The difference between RFS and TTR lies in the fact that all deaths—regardless of the cause of death—are counted as RFS events, whereas only deaths caused by the disease are counted as TTR events. For cases with documented relapse and missing relapse date, the date of relapse is substituted by the death date or the last follow-up date, if the patient is still alive. For all time-to-event end points, if the relevant event was not observed, the last day of follow-up is taken as the censoring date. Landmark analyses at different time points were used for exploring the association of OS with RFS and TTR.

Cox proportional hazards regression was used to model the association of the time-to-event end points with the characteristics of interest and estimate hazard ratios (HRs) along with their corresponding 95% confidence intervals. In multivariate models, using the backward selection method, with removal criterion of 10%, the association with outcome of each factor in the presence of others in the model was explored. Observed differences in time-to-event end points were depicted via Kaplan–Meier curves. Median follow-up time was estimated using the reverse censoring method for OS.

Cumulative incidence plots were created to explore time-to-local and time-to-distant recurrence.[5] Patients with missing site of relapse were excluded from this analysis, whereas patients with both types of recurrence were considered as having distant recurrence.

RESULTS

As of March 11, 2013, a total of 2449 retrospective cases of NSCLC have been captured in the Lungscape iBiobank (Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/JTO/A687). For all patients, surgery was performed no later than 2009 (91.5% with surgery from 2003 to 2009), and complete information was available on medical history, histology, and pathological TNM staging. Almost all patients with status alive at last follow-up have been followed for more than 3 years, with the exception of 43 patients with follow-up between 2 and 3 years.

Patient, Tumor, and Treatment Characteristics

The majority of patients are men (65.4%), with median age at surgery of 66 years (range, 23–90 years), and of white ethnicity (93.9%). Most are characterized as either current (31.9%) or former smokers (49.8%), whereas 13.8% are recorded as never smokers. Smoking history is unknown for only 4.5% of patients. Performance status (PS) at diagnosis is captured for 52.1% of the cohort, and the overwhelming

