BRIEF REPORT

Prognostic Value of Clinical Staging According to TNM in Patients With SCLC: A Real-World Surveillance Epidemiology and End-Results Database Analysis

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ABSTRACT

Introduction: SCLC is one of the most lethal malignancies. Classically, staging has been performed using a dual classification distinguishing limited from the extensive stage. This study aimed to evaluate the prognostic value of TNM staging in a real-world population of patients with SCLC.

Methods: Patients were selected from the Surveillance Epidemiology and End Results database. Chi-square bivariate analysis was used for the association of binary qualitative variables. A multivariate Cox regression analysis was performed to determine the impact of these prognostic factors on median overall survival (mOS) and long-term survival.

Results: A total of 26,221 patients were included (50.7% men, 55.7% ≥65 y, 82% White). At diagnosis, 18,574 (70.83%) presented metastases, which were more frequent in the liver (n = 11,896, 64%). In the overall population, mOS was 8 (7.86–8.14) months, which decreased according to each increasing category of TNM staging ($p < 0.0001$). The worse mOS was found among patients with stage IV SCLC (6 mo, 95% confidence interval: 5.83–6.17). Long-term survival decreased according to TNM staging, with patients having stage IV SCLC exhibiting the lowest survival rates at all follow-up time points. Within stage IV, the lowest mOS values were found in patients greater than or equal to 65 years and in those with liver metastases. Among the TNM stages corresponding to the limited stage, stage IB revealed the lowest hazard ratios value for risk of death compared with stage IA (hazard ratio = 1.161, 95% confidence interval: 0.97–1.40, $p = 0.114$), which increased gradually within the limited-stage SCLC. In the multivariate

analysis, TNM staging, male sex, and older age resulted in poor prognostic factors for survival.

Conclusions: TNM staging seems to define prognosis in patients with SCLC in the real-world setting, particularly for those patients with earlier disease.

Introduction

Lung cancer is the current leading cause of cancer worldwide.[1] The main subtypes of lung cancer on the basis of histopathological classification are SCLC and NSCLC, accounting for 15% and 85% of all cases, respectively.[2] In particular, SCLC is one of the most lethal malignancies characterized by rapid growth and early metastatic widespread, which causes most cases (70%) to present with advanced disease (extensive stage [ES]) at diagnosis.[2] For several decades, first-line chemotherapy for ES-SCLC with etoposide combined with platinum (cisplatin or carboplatin) has been the standard of care.[3] Despite the initial highly-favorable responses (up to 75%), most patients with ES-SCLC progress during the first months, resulting in a median overall survival (mOS) of 6 months (5.83–6.17). For limited disease, the mOS has been historically 14 months (13.6–14.4).[2] Recently, immunotherapy has opened up a new horizon in the SCLC therapeutic landscape, increasing mOS and long-term survival (LTS) in patients with ES-SCLC.[4]

Treatment for SCLC is usually determined by staging, which, historically, has been based on the Veterans Administration Lung Study Group system that defined SCLC as limited or extensive disease.[5] The International Association for the Study of Lung Cancer (IASLC) changed this system to consider as limited-stage (LS) SCLC all tumors in one hemithorax with lymph node metastases.[6] These classifications have a pragmatic approach as they divide patients according to the therapeutic strategy as to whether or not it included radiotherapy. In these staging systems, all patients with LS from I to III fall into the same category but exhibit different outcomes. Accurate staging of patients with SCLC would be helpful for diagnosis and decision-making on treatment.

Traditionally, the TNM classification system for the staging of cancer[7] has been one of the most reproducible prognostic factors. Stage, then, is a powerful prognostic variable that integrates the information included in the three separate prognostic factors: tumor size (T), nodal (N), and metastatic (M) involvement (number of metastasis and location).8 For patients with SCLC, although TNM has already been recommended as the preferred staging system by the IASLC,[9] this recommendation was done in a population enriched for surgical cases, which is not the usual treatment strategy nor the most frequent population in SCLC.[10,11]

This study aimed to evaluate the prognostic value of TNM staging for mOS and LTS in a real-world population of patients with SCLC.

Materials and Methods

This was a retrospective analysis including patients from the Surveillance Epidemiology and End Results (SEER) database.[12] Patients diagnosed between 2010 and 2015 with SCLC were selected. TNM staging was performed according to the seventh edition of the American Joint Committee on Cancer staging manual.[7] This study did not require informed consent.

Demographic characteristics of patients (age, sex, and race), primary tumor site and metastases, and mOS and LTS according to TNM clinical staging were collected. Survival time was considered as the time between diagnosis and death or the last follow-up time according to the SEER program definition. OS was defined as the time from the date of diagnosis to death of any cause.

Data are presented as frequencies (percentage) or median deviation (range). One-way analysis of variance was performed for comparisons of continuous variables. Chi-square bivariate analysis was used for the association of binary qualitative variables. The OS was analyzed on the basis of the above-mentioned parameters and the clinical stage, using the Kaplan-Meier method and the log-rank test comparing survival in two or more groups. A multivariate Cox regression analysis was performed measuring the effect by hazard ratios (HRs) and their 95% confidence intervals (CIs) to determine the impact of TNM staging, age, and sex on OS. A two-sided p value less than 0.05 was taken as statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences version 20.0 software.

Results

A total of 26,221 patients were included in this study. Among all patients, 13,306 (50.7%) were men, 14,598 (55.7%) were at least 65 years old, and 21,489 (82%) were White (Supplementary Table 1). At diagnosis, 18,574 (70.83%) were classified as stage IV. Metastasis frequently
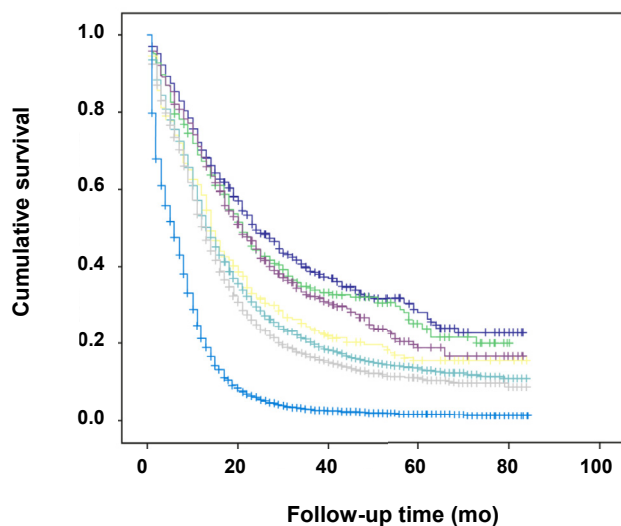
TNM stage	mOS (mo)	95% CI
⊓ Stage IA	24.00	20.50−27.50
⊓ Stage IB	21.00	17.84−24.16
⊓ Stage IIA	21.00	17.96−24.04
⊓ Stage IIB	14.00	12.41−15.60
⊓ Stage IIIA	14.00	13.37−14.63
⊓ Stage IIIB	13.00	12.41−13.59
⊓ Stage IV	6.00	5.83−6.17

Figure 1. Survival analysis according to TNM staging. OS decreased according to TNM staging. Stage IV patients revealed the lowest mOS values. CI, confidence interval; mOS, median overall survival; OS, overall survival.

involved the liver (n = 11,896, 64%), followed by bone (n = 8760, 47.2%), and brain (n = 6256, 33.7%). Furthermore, among cases with LS (I–III), most patients presented with stage III (20%), and only a small fraction of patients (5.6%) presented with early disease (stage I–II).

In the overall population, mOS was 8 (7.86–8.14) months. Specific survival analyses were performed to determine differences on the basis of TNM staging. As illustrated in Figure 1, mOS decreased according to TNM staging ($p < 0.0001$). The poorest mOS was found among patients with stage IV SCLC (6 mo, 95% CI: 5.83–6.17)—significantly shorter compared with patients with stage I to III, whose mOS was 14 months (95% CI: 13.60–14.41, $p < 0.0001$). Among cases that would fall into the LS category, we found a significant increase in the risk of death (Fig. 1 and Table 1) with each additional staging category (except for Stage IA, $p = 0.114$).

In terms of survival rates, LTS decreased over time and according to TNM staging, such that patients with stage IA SCLC exhibited a 28.1% survival rate at 5 years, whereas this figure decreased to 1.6% at 5 years for those with stage IV SCLC (Table 2). Finally, a multivariate Cox regression analysis was performed to determine the impact of TNM staging, age, and sex on OS. As presented in Table 1, TNM staging was an independent prognostic factor for survival. Thus, compared with the reference group (stage IA), patients with ES-SCLC (stage IV) revealed the poorest prognosis (HR = 3.684, 95% CI: 3.25–4.17, $p < 0.0001$). Regarding sex and age, women presented a reduced risk of death as compared with men (HR = 0.88, 95% CI: 0.86–0.90, $p < 0.0001$), whereas older age ($\geq$65 y as compared with <65 y) was independently associated with decreased OS (HR = 1.43, 95% CI: 1.40–1.47, $p < 0.0001$).

Table 1. Multivariate Cox Regression Analysis			
Variables	HR	95% CI	*p*-Value
Age ($\geq$65 y)	1.432	1.395-1.471	<0.0001
Female sex	0.880	0.86-0.90	<0.0001
TNM stage			
Stage IA	Reference group		
Stage IB	1.161	0.97-1.40	0.114
Stage IIA	1.193	1.00-1.41	0.046
Stage IIB	1.503	1.25-1.80	<0.0001
Stage IIIA	1.676	1.47-1.91	<0.0001
Stage IIIB	1.824	1.60-2.08	<0.0001
Stage IV	3.684	3.25-4.17	<0.0001

CI, confidence interval; HR, hazard ratio.

Table 2. Long-term Survival According to TNM Staging

Survival rates	Stage IA, %	Stage IB, %	Stage IIA, %	Stage IIB, %	Stage IIIA, %	Stage IIIB, %	Stage IV, %
6 mo	85.4	79.6	82.1	74.3	75.6	73.7	47.7
1 y	70.5	67.5	68.4	58.6	53.4	50.4	21.6
2 y	49.7	44.4	44.8	32.3	29.6	25.0	5.9
5 y	28.1	25.1	19.0	15.6	13.6	11.0	1.6

Within patients with stage IV disease, mOS was lower in those older than 65 years (4 mo [3.83–4.16] versus 8 mo [7.80–8.19]), and the presence of liver metastases was associated with the lowest mOS (4 mo [3.79–4.21]) (Supplementary Table 2).

Discussion

Without treatment, SCLC presents the most aggressive clinical course of all lung cancer types. Despite the advances in the field, therapeutic options remain limited and, contrary to NSCLC, the 5-year survival rate for patients with SCLC has not improved in the previous years. Identifying prognostic factors may help to design individualized treatment plans to improve efficacy outcomes and patients' quality of life, and also to reduce the incidence of adverse effects. In this study, we have confirmed TNM staging as a prognostic factor for OS in a real-world population of patients with SCLC. To our knowledge, this is the largest database analysis of patients with SCLC classified according to TNM staging.

In 2007, the analysis of a large database within the IASLC Lung Cancer Staging Project including 12,620 SCLC cases (TNM staging was available for 3430 cM0 patients and a complete pathologic TNM staging for 343 cases) revealed that increasing T, N, and stage (sixth and seventh editions) was associated with progressively lower survival.[11] A consensus report on SCLC staging and prognostic factors published in 1989 already recommended the use of the TNM staging system.[13] However, this system was never established. In the real-world setting, the analysis of 4884 patients from the SEER database diagnosed between 1998 and 2000 allowed the authors to conclude that the TNM stage should be used for stratifying patients with stage I to III in clinical trials.[8] Our study, conducted with a larger population from the same database, not only supports the prognostic value of TNM staging but specifically identifies clear differences in outcome for those patients categorized classically as LS. Currently, therapeutic innovations are being tested in clinical trials in LS (NCT03703297, NCT03540420, NCT03811002, NCT4308785). It would be relevant to include TNM staging as a stratification factor, as therapies might not be equally effective in patients with stage I to III. In this regard, it is worth noting that, in a real-world setting, some stage IV patients could be misdiagnosed as stage III because a positron emission tomography scan is not used to diagnose all patients with SCLC. Interestingly, we also observed that older patients, as compared with younger patients, and those with liver metastases, presented the lowest mOS values, confirming previous results in which both age and the presence of liver metastases had been identified as independent poor prognostic factors for OS in patients with ES-SCLC.[14,15] In the overall population, our multivariate analysis revealed the prognostic value of age and sex. Regardless of their stage, female patients presented a reduced risk of death, as previously reported by other authors.[16]

This study also has certain limitations owing to its retrospective nature. In addition, it was not possible to confidently exclude confounding factors, such as smoking history, metastatic sites such as the brain, which is a known prognostic factor, and treatments received, all owing to unavailable data. In this regard, we could assume most of the patients would have a history of tobacco exposure. Moreover, brain metastases could not be analyzed because brain computed tomography scans or magnetic resonance imaging were not performed in all patients at diagnosis. Thus, the lack of data did not allow any further analysis. It is also worth noting that the SEER database did not include Eastern Cooperative Oncology Group data, a well-established prognostic factor. However, patients with SCLC usually receive treatment regardless of the Eastern Cooperative Oncology Group level, which improves their performance status. Finally, the TNM staging of the patients included in the study may have not been accurate owing to the different diagnostic workups performed in different settings, and, therefore, some patients may be misclassified. This information will need to be collected in future prospective studies.

In conclusion, in the real-world setting, TNM staging was found to have a prognostic value for OS in patients with SCLC. This result highlights the importance of performing clinical staging according to TNM as recommended by the IASLC, because it may subclassify patients more precisely, especially in LS-SCLC. Finally, given the lack of survival improvements in the past years, new therapeutic strategies are required for these patients.

CRediT Authorship Contribution Statement

Acknowledgments

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2021.100266.

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