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RESEARCH ARTICLE

Failure patterns and the influence of the TNM staging systems on prognosis in limited disease small cell lung Cancer (SCLC): the Turkish Oncology Group (TOG) study

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Abstract

Purpose To determine recurrence patterns and prognostic factors in limited disease SCLC (LD-SCLC) and evaluate the effect of TNM classification on prognosis.

Material and Methods We retrospectively evaluated 266 patients with LD-SCLC who underwent curative chemoradiotherapy ± prophylactic cranial irradiation (PCI) between 2003 and 2016. These patients were recruited from 10 centers and restaged using the 7th and 8th TNM staging systems. We assessed the impact of TNM stage, age, gender, and PCI on all survival outcomes through univariate and multivariate analyses. Survival rates were calculated using the Kaplan–Meier method.

Results The median follow-up period was 42 months. In all cases, the 2- and 5-year local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and overall survival (OS) rates were 63.4–41.8%, 50.6–43.2%, and 50.9–27.7%, respectively. In the Cox regression analysis, N2-N3 disease and not receiving PCI were identified as poor prognostic factors for DMFS. In contrast, N2 disease, T4 stage according to the 8th TNM system, not receiving PCI, and thoracic RT doses < 60 Gy were recognized as prognostic factors negatively associated with OS. It was also observed that having N3 disease increases the risk of developing brain metastasis (BM) by a factor of 2.6.

Conclusion In our cohorts, the N category emerged as the most significant prognostic factor for overall survival, distant metastasis-free survival, and the development of brain metastasis. Considering that the definition of limited disease encompasses a broad spectrum of patients, TNM staging may be more beneficial in predicting patient prognosis and guiding treatment decisions, as suggested.

Keywords Small cell lung cancer · Stage · TNM staging · Limited disease

Introduction

Today, lung cancer still ranks first among solid tumors for incidence and mortality. Although small cell lung cancer (SCLC) accounts for only 15% of all lung cancers, it is often diagnosed at an advanced stage due to its aggressive nature and ability to metastasize rapidly, and it is highly fatal [1, 2]. The standard treatment consists of etoposide, platinum-based chemotherapy, and mediastinal radiotherapy / prophylactic cranial irradiation (PCI). Recent trials indicate combining immunotherapy with traditional treatments enhances treatment outcomes [3]. Currently, treatment guidelines recommend local curative treatments such as surgery and stereotactic body radiotherapy (SBRT) for patients diagnosed at an early stage (T1-T2, N0) [4–6]. Therefore, accurate and complete staging is increasingly important for treatment decisions and prognosis. [7].

Currently, the dual classification established by the Veterans Administration Lung Study Group (VALSG) in the 1950s is used for staging. The patients were divided clinically into limited disease (LD) and extensive disease (ED). The LD definition includes patients whose primary tumor and nodal involvement are confined to one hemithorax, who have no extrathoracic disease, and who can be safely treated with curative radiotherapy using a single radiation portal

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[8–10]. This staging has been widely accepted and used for many years because it is practical. However, it includes a heterogeneous group of patients ranging from stage I to III with positive or negative lymph nodes, and the prognosis of these patients is different for each group. Therefore, it is no longer sufficient for accurate and complete staging and treatment planning in today's conditions.

In 2007, the SCLC Subcommittee of the International Association for the Study of Lung Cancer (IASLC) recommended using the tumor-node-metastasis (TNM) staging system instead of the VALSG staging system, especially in SCLC patients with LD [11, 12].

Meanwhile, the existing 7th TNM staging system was updated and made more detailed following the inclusion of PET/CT in clinical staging, and the 8th TNM staging system was published in 2016 [12]. Subsequent validation studies have emphasized the critical role of the TNM staging system in providing prognostic information in SCLC and confirmed that it is a determinant of survival in a large group of patients [13–17].

We aimed to determine the recurrence patterns and prognostic factors in patients with LD-SCLC who underwent definitive chemoradiotherapy ± PCI and evaluate the effect of TNM staging on prognosis.

Materials and methods

Study protocol

This project is a national, multicenter, retrospective study designed within the Turkish Oncology Group (TOG) Lung Cancer Study Subgroup. The institutional review board at each participating center approved the study protocol, which was conducted under the Declaration of Helsinki. Furthermore, all patients provided written consent.

Patients' selection

Between January 2003 and December 2016, 266 patients with LD-SCLC who received definitive chemoradiotherapy (CRT) ± PCI at ten oncology centers were assessed. The inclusion criteria for the study were as follows: (1) having a histologically diagnosed SCLC; (2) the presence of limited disease staged radiologically and clinically; (3) treated with definitive concurrent or sequential chemotherapy plus radiotherapy (RT); (4) radiotherapy was delivered with three-dimensional conformal radiotherapy (3D-CRT) or Intensity Modulated Radiation Therapy (IMRT) technique; (5) Eastern Cooperative Oncology Group (ECOG) performance status scale ≥ 2, (6) regular follow-up of patients, and (6) absence of any previous cancer diagnosis or treatment history. Patients diagnosed with NSCLC, aged < 18 years, with metastatic disease, who had received postoperative RT or a history of RT, with a second malignancy, and a poor ECOG score were excluded from the study.

All patients' medical records and treatment data were retrieved from archived files and radiotherapy charts. Patients were restaged using their initial chest/abdominopelvic computed tomography (CT) scans and/or 18-fluorodeoxyglucose positron emission tomography combined with computed tomography (^{18}FDG PET/CT) according to both the 7th and 8th TNM staging systems. In addition, each patient underwent contrast-enhanced magnetic resonance imaging (MRI) of the brain at diagnosis to rule out the presence of brain metastases.

Treatment characteristics

Patients were treated with systemic chemotherapy (concurrent or sequential) and thoracic radiotherapy with curative intent, followed by PCI in eligible patients. Systemic therapy consisted of a total of 4–6 cycles of cisplatin (at 25 or 75 mg/m^2) and etoposide (at 100–120 mg/m^2) every 3–4 weeks, concurrently or sequentially (according to the patient's condition and the treatment protocol of the participating centers). In patients who could not receive cisplatin, carboplatin area under the curve (AUC) 5–6 day one and etoposide 100 mg/m^2 were used instead. For concurrent treatment, thoracic radiotherapy was started on the second or third cycle of chemotherapy.

Of the patients, 132 (49.6%) received thoracic radiotherapy using the 3D-CRT technique, while 50.4% were irradiated using the IMRT technique. The total thoracic RT dose is varied between 30 and 66.8 Gy, according to each centre's treatment schedules, with conventional fractionation. After completing all treatments, PCI was performed in patients who had no brain metastases on contrast-enhanced cranial MRI and were eligible for treatment.

Follow-up and outcomes assessment

After all treatments were completed, patients were followed up with clinical examinations and chest CT scans every three months for the first two years, then every six months until the fifth year, and annually after the fifth year. Further investigations were performed with contrast-enhanced brain MRI if clinically necessary, and PET/CT in case of suspicion of recurrence or metastasis.

The trial's endpoints were local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and overall survival (OS). Local recurrence-free survival was defined as the time from diagnosis to local recurrence or event. Distant metastasis-free survival was between diagnosis and the first occurrence of distant metastatic disease or the last control date. Overall survival was considered the time from

the date of diagnosis to the last control visit or death from any cause.

Statistical methods

Statistical analyses of the study were performed with SPSS version 22.0 (SPSS for Windows, IBM Corp., Armonk, NY, USA). Descriptive data are presented as a mean value, a median value, or a number and a frequency. All survival analyses were performed using the Kaplan–Meier method. Comparisons were made using the log-rank test. The effect of age, gender, stage, chemotherapy, thoracic RT dose, using PET/CT for staging, and prophylactic cranial irradiation on survival was analyzed in univariate analysis with the Kaplan–Meier method and the log-rank test. Prognostic factors found to be statistically significant in the univariate analysis were re-evaluated using a multivariate Cox regression analysis. A p value < 0.05 was considered to be significant.

Results

Patients and treatments

Data from 266 patients with LD-SCLC treated curatively at ten different oncology centers were analyzed. The median follow-up was 42 months (range, 5 and 129 months). The median age was 59.5 years (range 30–86), and most patients were male (n: 222, 83.5%).

In 205 of the 266 patients, TNM staging was performed using initial PET/CT and cranial MRI. There were 13 cases (4.9%) in T1, 94 cases (35.3%) in T2, 94 cases (35.3%) in T3, and 65 cases (24.4%) in T4 according to the 7th TNM. Under the 8th TNM system, there were 25 cases (9.4%) in T1, 83 cases (31.2%) in T2, 56 cases (21.1%) in T3, and 102 cases (38.3%) in T4. In the 8th edition, the number of T2 and T3 cases decreased, while the number of T1 and T4 cases increased, particularly the number of T1 cases almost doubled. A total of 214 patients (80.5%) were lymph node-positive. Of these 214 cases, 10.5% were in the N1 stage, 52.6% in the N2 stage, and 17.3% in the N3 stage.

According to the 7th TNM staging system, the stage distribution was as follows: in stage I, 24 (9%) patients; in stage II, 31 (11.7%) patients; and in stage III, 211 (79.3%) patients. Similarly, according to the 8th TNM staging system, there were 18 patients in stage I (6.8%), 31 patients in stage II (11.7%), and 217 patients in stage III (81.6%). Most of the patients were clustered in stage III.

Concurrent chemoradiation was administered to 113 of the patients. The median dose of thoracic radiotherapy was 60 Gy (30–66.8 Gy) and 134 patients received ≥ 60 Gy. PCI was performed in 181 (68%) patients at a median of one month after thoracic RT. In 58% of the patients who underwent PCI, 25 Gy was delivered in 10 fractions. The characteristics of the patients and treatments are listed in Table 1.

Local control (LRFS)

Local recurrence occurred in 98 patients (36.8%); the median LRFS was estimated to be 37 months. While 53 patients had isolated local recurrence, 45 had local and distant disease. In the overall cohort, 2-year and 5-year LRFS were 63.4% and 41.8%, respectively.

In univariate analysis, the presence of PET/CT for staging improved LRFS rates, while there was a positive trend between good performance status and LRFS ($p = 0.068$). Similarly, PET/CT staging was the most significant prognostic factor for local recurrence in the Cox regression analysis. In contrast, no significant association was observed between stage, T, and N categories and local recurrence (Table 2).

Distant metastasis (DMFS)

Distant metastases (DM) developed in 124 of 266 patients after a median of 26 (range 4–129) months. Among patients with metastases, 79 had isolated metastases. The 2-year and 5-year DMFS were 50.6% and 43.2%, respectively. In univariate analysis, the patients with smaller T and N stages according to the 8th TNM, with stage I-II disease according to the 7th and 8th TNM, those had PET-CT for staging, treated by thoracic RT ≥ 60 Gy, and had PCI was found to be significantly better DMFS (Table 3). In the multivariate analysis, the most important factors that increased the risk of distant metastasis were the N2-3 nodal stage and the no PCI (Table 3). In particular, the N3 stage has been shown to increase the likelihood of distant metastasis by approximately 3.3 times.

The most common distant metastases were located in the brain, followed by bone and liver. A total of 66 patients (24.8%) developed brain metastasis (BM), with 95.4% occurring within the first two years. While 44 patients had only brain metastases, 22 had both brain and systemic metastases, and the remaining 58 had systemic metastases only. Moreover, 31 (47%) patients with BM had not previously undergone PCI. Among the 66 patients with brain metastases, 58 (88%) were classified in the stage III group according to the 7th and 8th TNM classification system. The risk of developing BM was observed to be linked to the N categories, with the risk increasing 2.6-fold in N3 disease.

Survival outcomes (OS)

At analysis, 109 patients were still alive, having survived a median of 25 months (range 5–129). All patients' overall

Table 1 Baseline patients and treatment characteristics

Variables	*n*	(%)
Age at diagnosis (year)	median 59.5	(range:30–86)
Age group		
≤ 60y	153	(57.5)
> 60y	113	(42.5)
Gender		
Male	222	(83.5)
Female	44	(16.5)
ECOG Performance status		
0	120	(45.1)
1–2	146	(54.9)
Staging		
With PET/CT	205	(77.1)
With conventional imaging	61	(22.9)
Tumor stage (7th TNM ed.)		
T1	13	(4.9)
T1a	7	(2.6)
T1b	6	(2.3)
T2	94	(35.3)
T2a	67	(25.2)
T2b	27	(10.2)
T3	94	(35.3)
T4	65	(24.4)
Tumor stage (8th TNM ed.)		
T1	25	(9.4)
T1a	3	(1.1)
T1b	9	(3.4)
T1c	13	(4.9)
T2	83	(31.2)
T2a	40	(15.0)
T2b	43	(16.2)
T3	56	(21.1)
T4	102	(38.3)
N stage		
N0	52	(19.5)
N1	28	(10.5)
N2	140	(52.6)
N3	46	(17.3)
Stage (7th TNM ed.)		
IA	5	(1.9)
IB	19	(7.1)
IIA	16	(6.0)
IIB	15	(5.6)
IIIA	132	(49.6)
IIIB	79	(29.7)
Stage (8th TNM ed.)		
IA1	2	(0.8)
IA2	1	(0.4)
IA3	6	(2.3)
IB	9	(3.4)
IIA	8	(3.0)
IIB	23	(8.3)
IIIA	88	(33.1)
IIIB	95	(35.7)
IIIC	34	(12.8)
Chemotherapy		
Concurrently	113	(42.5)
Sequential	87	(32.7)
Missing	66	(24.8)
Total CT cycles	3 (range 2–6)	
Thoracic radiotherapy dose	median 60 Gy	(range: 30–66.8 Gy)
RT dose		
< 60 Gy	132	(49.6)
≥ 60 Gy	134	(50.4)
RT technique		
3D-CRT	130	(48,9)
IMRT	136	(51.1)
Fractionation	median 2 Gy	(range: 1.5–3 Gy)
PCI		
Yes	181	(68)
No	85	(32)
PCI dose		
25 Gy	105	(58)
30 Gy	76	(42)

survival (OS) rates were 50.9% and 27.7% at two and five years, respectively.

When patients were evaluated according to the 7th and 8th TNM staging systems, the median overall survival (mOS) and the 1–2-3 and 5-year survival rates decreased gradually with increasing stages (Fig. 1a–b). According to the 7th edition, the mOS decreased from 45 months for stages I–II to 22 months for stage III. Similarly, in the 8th edition, the median survival declined from 55 months for stages I–II to 22 months for stage III (Table 4–5).

The T stage was evaluated as T1, T2, T3, and T4 in four main categories, the1-2–3 and 5-year survival rates decreased progressively from T1 to T4 in both TNM systems. Similarly, when nodal involvement was evaluated, all survival rates and mOS decreased from cN0 to cN3.

In univariate analysis, good performance status, thoracic RT dose ≥ 60 Gy, use of PET/CT for staging, presence of PCI, N0 disease, smaller T stage according to the 8th staging system, and early-stage disease according to both the 7th and 8th staging systems were found to be prognostic factors that positively affected OS (Table 6). In multivariate analysis, the T4 category according to 8th TNM, N2 disease, thoracic RT dose was < 60 Gy and no

Table 2 Univariate and multivariate analyses for local recurrence free-survival

Variables	Univariate model		Multivariate model	
	HR (95%CI)	p	HR (95%CI)	p
Age				
≤60	1 (ref)			
>60	1.038 (0.693–1.554)	0.856	–	–
Gender				
Male	1 (ref)			
Female	0.974 (0.583–1.627)	0.920	–	–
Performance status				
ECOG 0	1 (ref)		1 (ref)	
ECOG 1–2	1.452 (0.967–2.182)	0.072	1.359 (0.899–2.052)	0.145
T stage (7th TNM)		0.828		
T1	1 (ref)		–	–
T2	1.112 (0.468–2.642)	0.810		
T3	1.023 (0.428–2.446)	0.960		
T4	0.861 (0.347–2.133)	0.746	–	
T stage (8th TNM)		0.271		
T1	1 (ref)		–	–
T2	1.310 (0.628–2.729)	0.471		
T3	1.916 (0.912–4.029)	0.086		
T4	1.680 (0.817–3.458)	0.159		
N stage		0.779		
N0	1 (ref)		–	–
N1	1.224 (0.612–2.447)	0.568		
N2	1.309 (0.779–2.199)	0.309		
N3	1.139 (0.574–2.259)	0.711		
Stage (7th TNM)				
Stage I–II	1 (ref)		–	–
Stage III	0.727 (0.444–1.191)	0.205		
Stage (8th TNM)				
Stage I–II	1 (ref)		–	–
Stage III	1.210 (0.741–1.974)	0.447		
Staging with PET/CT				
Yes	1 (ref)		1 (ref)	
No	1.740 (1.128–2.683)	0.012	1.650 (1.064–2.559)	0.025
Chemotherapy				
Concurrent	1 (ref)		–	–
Sequential	1.355 (0.882–2.683)	0.166		
Thorasic RT dose				
≥60 Gy	1 (ref)		–	–
<60 Gy	1.345 (0.903–2.004)	0.145		
RT Technique				
3D-CRT	1 (ref)	0.347	–	
IMRT	1.213 (0.811–1.814)			
PCI				
Yes	1 (ref)		–	–
No	1.270 (0.807–2.000)	0.302		

PCI were poor prognostic factors for OS (Table 4). N2 disease mainly affects overall survival. In contrast, the presence of N3 disease was found to be close to significant due to the small number of patients.

Table 3 Univariate and multivariate analyses for distant metastases free-survival

Variables	Univariate model		Multivariate model	
	HR (95%CI)	p	HR (95%CI)	p
Age				
≤60	1 (ref)		–	–
>60	0.799 (0.555–1.150)	0.227		
Gender				
Male	1 (ref)		–	–
Female	0.866 (0.536–1.399)	0.555		
Performance status				
ECOG 0	1 (ref)		–	–
ECOG 1–2	1.299 (0.907–1.859)	0.153		
T stage (7th TNM)		0.557		
T1	1 (ref)		–	–
T2	1.010 (0.428–2.383)	0.982		
T3	1.361 (0.581–3.184)	0.478		
T4	1.187 (0.495–2.845)	0.701		
T stage (8th TNM)		0.019		
T1	1 (ref)		1 (ref)	
T2	1.689 (0.784–3.638)	0.180	1.334 (0.612 – 2.908)	0.468
T3	1.877 (0.846–4.165)	0.122	1.314 (0.583 – 2.959)	0.510
T4	2.720 (1.293–5.723)	0.008	2.028 (0.954 – 4.308)	0.066
N stage		0.001		
N0	1 (ref)		1 (ref)	
N1	1.746 (0.830–3.671)	0.142	1.723 (0.815–3.641)	0.154
N2	2.305 (1.313–4.044)	0.004	2.120 (1.203–3.736)	0.009
N3	3.674 (1.961–6.883)	<0.0001	3.355 (1.751–6.426)	<0.0001
Stage (7th TNM)				
Stage I–II	1 (ref)		1 (ref)	
Stage III	1.802 1.115–2.912)	0.016	0.800 (0.337 – 1.902)	0.614
Stage (8th TNM)				
Stage I–II	1 (ref)		1 (ref)	
Stage III	2.674 (1.503–4.759)	0.001	1.245 (0.531–2.918)	0.615
Staging with PET/CT				
Yes	1 (ref)		1 (ref)	
No	1.526 (1.038–2.243)	0.032	1.480 (0.974 – 2.249)	0.067
Chemotherapy				
Concurrent	1 (ref)		–	–
Sequential	1.350 (0.907–2.011)	0.139		
Thorasic RT dose				
≥60 Gy	1 (ref)		1 (ref)	
<60 Gy	1.548 (1.084–2.211)	0.016	1.071 (0.722–1.588)	0.733
RT Technique				
3D-CRT	1 (ref)		–	
IMRT	0.914 (0.642–1.301)	0.617		
PCI				
Yes	1 (ref)		1 (ref)	
No	1.883 (1.303–2.722)	0.001	1.603 (1.080 – 2.379)	0.019
Local control				
Yes	1 (ref)		–	–
No	1.223 (0.847–1.765)	0.283		

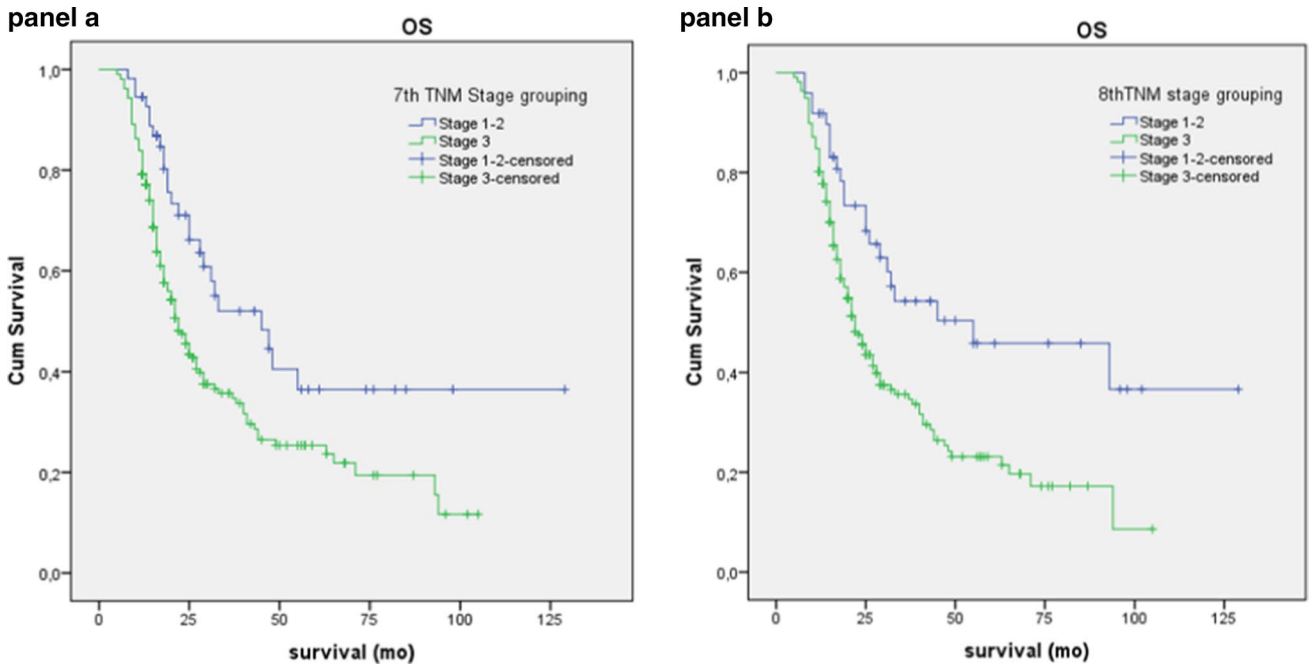


Fig. 1 **a** OS curve according to 7th TNM stage grouping. **b** OS curve according to 8th TNM stage grouping

Table 4 Overall survival rates according to the stages in the 7th TNM staging system

7th TNM Stage	event/n	mOS (months)	1 year OS (%)	2 year OS (%)	3 year OS (%)	5 year OS (%)
Stage 1–2	25/55	45	94.5	71	52	36.5
Stage 3	132/211	22	83.9	45.5	35.7	25.4

Table 5 Overall survival rates according to the stages in the 8th TNM staging system

8th TNM Stage	event/n	mOS (months)	1 year OS (%)	2 year OS (%)	3 year OS (%)	5 year OS (%)
Stage 1–2	22/49	55	91.8	73.4	54.2	45.8
Stage 3	135/217	22	80.2	45.6	35.6	23.1

Discussion

Although treatment outcomes have improved to some extent with new options like targeted therapies and immunotherapy, survival rates remain low for most SCLC patients. Nonetheless, recent studies indicate benefits for some patients from surgery, stereotactic ablative radiotherapy, and immunotherapy [18–25]. More information on accurate prognostic factors can help clarify which groups of patients will benefit from these treatment schedules. In the TNM system, the T and N classifications offer more detailed insights into the primary tumor and its spread compared to the Veterans classification. Firstly, Stahel et al. [26] recommended a consensus report on the use of TNM staging in 1989; subsequently, in 2007, IASCLC demonstrated the prognostic value of TNM staging [11]. Notably, in the last two TNM staging systems, dividing the T stage into subgroups based on the primary tumor size has revealed slight differences in tumor size concerning prognosis and enhanced prediction [11, 12]. In our series, the number of T1 patients in the 8th TNM staging nearly doubled compared to the 7th TNM staging. More accurate and precise detection of T1 tumors will help identify patients who are candidates for surgery and enhance survival rates.

In our study, we aimed to validate the latest two TNM staging systems for patients with LD-SCLC, investigate the impact of TNM stage on prognosis, and define recurrence patterns among Turkish patients.

Table 6 Univariate and multivariate analyses for overall survival

Variables	Univariate model		Multivariate model	
	HR (95%CI)	p	HR (95%CI)	p
Age				
≤60	1 (ref)		–	–
>60	0.989 (0.719–1.360)	0.944		
Gender				
Male	1 (ref)		–	–
Female	0.823 (0.539–1.257)	0.368		
Performance status				
ECOG 0	1 (ref)		1 (ref)	
ECOG 1–2	1.548 (1.122–2.135)	0.008	1.141 (0.809–1.609)	0.453
T stage (7th TNM)		0.752		
T1	1 (ref)			
T2	0.947 (0.466–1.925)	0.880	–	–
T3	1.078 (0.531–2.188)	0.835		
T4	1.182 (0.576–2.426)	0.648		
T stage (8th TNM)		0.007		
T1	1 (ref)		1 (ref)	
T2	2.246 (1.132–4.455)	0.021	1.898 (0.951–3.790)	0.069
T3	2.171 (1.064–4.431)	0.033	1.668 (0.807–3.444)	0.167
T4	3.100 (1.583–6.068)	0.001	2.686 (1.365–5.286)	0.004
N stage		0.003		
N0	1 (ref)		1 (ref)	
N1	1.200 (0.629–2.290)	0.580	1.090 (0.568–2.092)	0.796
N2	1.975 (1.252–3.115)	0.003	1.604 (1.006–2.558) 1.643 (0.946–2.852)	0.047
N3	2.411 (1.412–4.118)	0.001		0.078
Stage (7th TNM)				
Stage I–II	1 (ref)		1 (ref)	
Stage III	1.879 (1.224–2.885)	0.004	1.150 (0.571–2.316)	0.696
Stage (8th TNM)				
Stage I–II	1 (ref)		1 (ref)	
Stage III	2.068 (1.309–3.264)	0.002	0.861 (0.413–1.797)	0.690
Staging with PET/CT				
Yes	1(ref)		1 (ref)	
No	1.476 (1.049–2.078)	0.026	1.225 (0.842–1.782)	0.290
Chemotherapy				
Concurrent	1 (ref)		–	–
Sequential	1.334 (0.938–1.898)	0.109		
Thorasic RT dose				
≥60 Gy	1 (ref)		1 (ref)	
<60 Gy	1.887 (1.367–2.603)	<0.0001	1.581 (1.122–2.228)	0.009
RT Technique				
3D-CRT	1 (ref)		–	
IMRT	0.846 (0.614–1.165)	0.306		
PCI				
Yes	1 (ref)		1 (ref)	
No	2.026 (1.456–2.820)	<0.0001	1.681 (1.175–2.403)	0.004
Local control				
Yes	1 (ref)		–	–
No	0.774 (0.565–1.060)	0.110		

Same as NSCLC, TNM staging is an independent prognostic factor for survival in SCLC. The SEER data reported by Arriola et al. [7], which included approximately 26,000 patients, demonstrated the relationship between TNM staging and survival, although most patients had metastatic disease.

In the present study, survival worsened with increasing stages. Although the number of patients in the stage groups was small, a significant relationship between survival and the stage of disease could not be demonstrated. However, median survival increased from 45 to 55 months, and 5-years OS was improved to 45,98% from 36,5% according to the 8th TNM; the effect on survival is quite large. Thus, we can say that 8th TNM staging is a valuable prognostic factor in distinguishing early stages. On the other hand, the analyses demonstrated that N2-N3 nodal involvement and T4 stage according to the 8th TNM have a negative impact on survival. The DMFS and OS were superior for the patients with T1 and N0-NI tumors than the others., Tan et al. [27] conducted a study in China that compared the 7th and 8th TNM staging systems in SCLC and reported that the 8th staging system showed a better prognosis. They also determined that the prognosis was worse in the presence of N3 disease. N2 disease was more common in our series, and the survival rate after N2 disease gradually deteriorated. In the presence of N3 disease, the probability of distant metastasis was 3.3 times higher, and the likelihood of developing BM was 2.6 times higher as well.

Considering this negative effect of the N stage on prognosis, the TNM staging system has been updated again, and the N category (especially N2 and N3) has been divided into subgroups in the 9th TNM staging system, which will be available soon [28]. Once validated for SCLC, more intensive treatment options may be considered for N2-N3 patients.

However, the TNM staging of SCLC is still not widely used in clinical practice for several reasons. There is limited evidence that treatment plans for patients with LS-SCLC should be modified based on the TNM stage. In addition, the lack of information on the pathological staging of most SCLC patients, together with the fact that many patients present at an advanced stage (stage III), has led to a preference for starting treatment with chemoradiotherapy due to the high risk of occult metastases in the early stages. This situation hinders the routine use of the TNM staging system [29].

Another critical issue is whether to perform PCI, which has recently become controversial due to its neurocognitive side effects and the possibility of a follow-up with a cranial MRI [29–32]. Early-stage disease can be better defined by using the TNM staging system. Among patients with a chance of cure and a long life expectancy, a group can be identified in which there is a low risk of BM, and PCI is not performed to avoid neurocognitive effects. According to the NCCN guideline version 2.2025 for SCLC, the benefit of PCI in very early-stage SCLC patients is unclear [33]. Similarly, the most recent clinical guidelines from ASTRO, ASCO, and ESMO also offer follow-up with MRI as an option for these patients [4, 34, 35]. In contrast, in our study, DMFS and OS were worse in patients who did not undergo PCI than in those who did. However, most of the patients who developed BM were in stage III, only 2 were in stage I, and approximately 80% of our patient group consisted of stage III patients.

One of the most important differences between the 7th and 8th TNM staging systems is the integration of the use of PET/CT into clinical staging in the 8th version. Thus, the 8th TNM staging system has been updated by correcting the deficiencies in the 7th edition. At present, PET/CT is widely used in the staging of lung cancer because it is non-invasive and can show metabolic activity. In a Japanese study by Ohno et al. [36], conventional imaging methods with FDG-PET/CT, PET/MRI, and whole-body MRI were prospectively compared in the staging of SCLC. According to the TNM staging system, the sensitivity and specificity of FDG-PET/CT in distinguishing stage I disease from other stages compared to conventional imaging methods are 84.6% vs. 61.5% and 98.8% vs. 100%, respectively. The positive and negative predictive values are 91.7% vs. 100% and 97.7% vs. 94.4%, respectively. The accuracy rate is 94.9% vs. 96.9%. A recent study by Graabak et al. [37] showed that using FDG-PET/CT for staging and RT planning in limited-stage SCLC patients reduced the acute toxicity from thoracic radiotherapy but did not affect OS and PFS. However, in our cohort, 77% of the patients had PET/CT, and LRFS results were better in patients whose initial staging was performed with PET. Patients staging with PET/CT probably achieved more accurate staging. We also think that using PET/CT in radiotherapy planning may have impacted local control by reducing the possibility of geographical misses.

Despite those mentioned above and known prognostic factors, survival outcomes remain relatively poor as the stage increases. SCLC is a distinct entity among lung cancers. Studies have reported intertumoral and intratumoral heterogeneity. How this heterogeneity affects the biology of the disease is being investigated [2]. Different subtypes of SCLC can be identified by understanding the genetic and biological molecular features. Perhaps, by incorporating biological molecular features into staging, as in breast and endometrial cancer, many different points can be reached in treatment and prognosis.

When evaluating our study, some shortcomings should also be taken into consideration. Firstly, it is a multi-institutional retrospective study. Second, patients were clinically staged based on available imaging modalities at diagnosis. Since there is no central verification, there may be differences between clinicians. Furthermore, variations

in treatment techniques and RT doses have been observed across time and between centres. Before 2010, patients were treated with 3D-CRT; subsequently, the majority were treated with IMRT. These factors also may have influenced survival outcomes. However, as the number of patients was relatively small, no statistically significant differences were observed in the survival analyses according to the technique used.

In contrast, all patients received standard treatment, such as concurrent or sequential chemoradiation, and 68% received PCI. Staging was performed using PET/CT in 77% of patients. The advantage of our study is that ten different experienced cancer centers from different regions across the country participated in the study. The results reflect the general picture as well as possible for our country, and this makes the results valuable.

Conclusion

Although the VALSG classification is practical for clinical routine, the TNM classification provides a more accurate and precise classification. The definition of limited-stage SCLC includes a wide range of patients. Identifying patients at very early stages (T1, N0) may increase the chance of cure with different treatment options. Therefore, clinicians and researchers should be encouraged to use the TNM staging system more widely. The N component is also very important. In the 9th staging system, the division of lymph node involvement into subgroups based on localisation and number in the TNM system will further reveal the difference in patients' prognosis for NSCLC; we have to wait for this edition to be validated for SCLC. The molecular and biological characteristics of SCLC have also been extensively studied recently. Perhaps a new update will further incorporate molecular features that will help to understand and differentiate the fundamental prognostic factors and treatment strategies.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48. https://doi.org/10.3322/caac.21763.
2. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primers. 2021;7(1):3. https://doi.org/10.1038/s41572-020-00235-0.
3. Wang Y, Zou S, Zhao Z, Liu P, Ke C, Xu S. New insights into small-cell lung cancer development and therapy. Cell Biol Int. 2020;44(8):1564–76.
4. Dingemans AC, Früh M, Ardizzoni A, Besse B, Faivre-Finn C, Hendriks LE, et al. Small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up☆. Ann Oncol. 2021;32(7):839–53. https://doi.org/10.1016/j.annonc.2021.03.207.
5. Daly ME, Ismaila N, Decker RH, Higgins K, Owen D, Saxena A, et al. Radiation therapy for small-cell lung cancer: ASCO guideline endorsement of an ASTRO guideline. J Clin Oncol. 2021;39(8):931–9. https://doi.org/10.1200/JCO.20.03364.
6. García-Campelo R, Sullivan I, Arriola E, Insa A, Juan Vidal O, Cruz-Castellanos P, et al. SEOM-GECP clinical guidelines for diagnosis, treatment and follow-up of small-cell lung cancer (SCLC). Clin Transl Oncol. 2023;25(9):2679–91. https://doi.org/10.1007/s12094-023-03216-3.
7. Arriola E, Trigo JM, Sánchez-Gastaldo A, Navarro A, Perez C, Crama L, et al. Prognostic value of clinical staging according to TNM in patients with SCLC: a real-world surveillance epidemiology and end-results database analysis. JTO Clin Res Rep. 2021;3(1):100266. https://doi.org/10.1016/j.jtocrr.2021.100266.
8. Micke P, Faldum A, Metz T, Beeh KM, Bittinger F, Hengstler JG, et al. Staging small cell lung cancer: veterans administration lung study group versus international association for the study of lung cancer–what limits limited disease? Lung Cancer. 2002;37(3):271–6. https://doi.org/10.1016/s0169-5002(02)00072-7.
9. Kalemkerian GP, Gadgeel SM. Modern staging of small cell lung cancer. J Natl Compr Canc Netw. 2013;11(1):99–104. https://doi.org/10.6004/jnccn.2013.0012.
10. Kalemkerian GP. Staging and imaging of small cell lung cancer. Cancer Imaging. 2012;11(1):253–8. https://doi.org/10.1102/1470-7330.2011.0036.
11. Shepherd FA, Crowley J, Van Houtte P, Postmus PE, Carney D, Chansky K, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol. 2007;2(12):1067–77. https://doi.org/10.1097/JTO.0b013e31815bdc0d.
12. Nicholson AG, Chansky K, Crowley J, Beyruti R, Kubota K, Turrisi A, Eberhardt WE, van Meerbeeck J, Rami-Porta R; Staging and Prognostic Factors Committee, Advisory Boards,

and Participating Institutions; Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(3):300–11. https://doi.org/10.1016/j.jtho.2015.10.008.
13. Erdoğu V, Çıtak N, Sezen CB, Aksoy Y, Aker C, Doğru MV, et al. Comparison of 6th,7th, and 8th editions of the TNM staging in non-small cell lung cancer patients: validation of the 8th edition of TNM staging. Turk Gogus Kalp Damar. 2022;30(3):395–403.
14. Tendler S, Grozman V, Lewensohn R, Tsakonas G, Viktorsson K, De Petris L. Validation of the 8th TNM classification for small-cell lung cancer in a retrospective material from Sweden. Lung Cancer. 2018;120:75–81. https://doi.org/10.1016/j.lungcan.2018.03.026.
15. Zhang W, Zhu H, Zhou Z, Feng Q, Chen D, Zhang H, et al. [Prognostic value of AJCC TNM staging 7th edition in limited-stage small cell lung cancer: validation in 437 patients]. Zhonghua Zhong Liu Za Zhi. 2015;37(12):917–22.
16. Jhun BW, Lee KJ, Jeon K, Suh GY, Chung MP, Kim H, et al. Clinical applicability of staging small cell lung cancer according to the seventh edition of the TNM staging system. Lung Cancer. 2013;81(1):65–70. https://doi.org/10.1016/j.lungcan.2013.03.005.
17. Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallières E, Groome P, et al. The IASLC lung cancer staging project: external validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. J Thorac Oncol. 2017;12(7):1109–21. https://doi.org/10.1016/j.jtho.2017.04.011.
18. Zhao X, Kallakury B, Chahine JJ, Hartmann D, Zhang Y, Chen Y, et al. Surgical resection of SCLC: prognostic factors and the tumor microenvironment. J Thorac Oncol. 2019;14(5):914–23. https://doi.org/10.1016/j.jtho.2019.01.019.
19. Wakeam E, Acuna SA, Leighl NB, Giuliani ME, Finlayson SRG, Varghese TK, et al. Surgery versus chemotherapy and radiotherapy for early and locally advanced small cell lung cancer: a propensity-matched analysis of survival. Lung Cancer. 2017;109:78–88. https://doi.org/10.1016/j.lungcan.2017.04.021.
20. Hoda MA, Klikovits T, Klepetko W. Controversies in oncology: surgery for small cell lung cancer? It's time to rethink the case. ESMO Open. 2018;3(3):e000366. https://doi.org/10.1136/esmoopen-2018-000366.
21. Safavi AH, Mak DY, Boldt RG, Chen H, Louie AV. Stereotactic ablative radiotherapy in T1–2N0M0 small cell lung cancer: a systematic review and meta-analysis. Lung Cancer. 2021;160:179–86. https://doi.org/10.1016/j.lungcan.2021.07.007.
22. Paximadis P, Beebe-Dimmer JL, George J, Schwartz AG, Wozniak A, Gadgeel S. Comparing treatment strategies for stage I small-cell lung cancer. Clin Lung Cancer. 2018;19(5):e559–65. https://doi.org/10.1016/j.cllc.2018.03.017.
23. Hellmann MD, Callahan MK, Awad MM, Calvo E, Ascierto PA, Atmaca A, et al. Tumor mutational burden and efficacy of Nivolumab monotherapy and in combination with Ipilimumab in small-cell lung cancer. Cancer Cell. 2019;35(2):329. https://doi.org/10.1016/j.ccell.2019.01.011.
24. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M, Reck M, Mok T, Lam S, Shames DS, Liu J, Ding B, Lopez-Chavez A, Kabbinavar F, Lin W, Sandler A, Liu SV; IMpower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220–2229.
25. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394(10212):1929–39. https://doi.org/10.1016/S0140-6736(19)32222-6.
26. Stahel R, Ginsberg R, Havemann K, et al. Staging and prognostic factors in small cell lung cancer: a consensus report. Lung Cancer. 1989;5:119–26.
27. Tan F, Bi N, Zhang H, Li R, Wang Z, Duan J, et al. External validation of the eighth edition of the TNM classification for lung cancer in small cell lung cancer. Lung Cancer. 2022;170:98–104. https://doi.org/10.1016/j.lungcan.2022.03.011.
28. Rami-Porta R, Nishimura KK, Giroux DJ, Detterbeck F, Cardillo G, Edwards JG, Fong KM, Giuliani M, Huang J, Kernstine KH Sr, Marom EM, Nicholson AG, Van Schil PE, Travis WD, Tsao MS, Watanabe SI, Rusch VW, Asamura H; Members of the IASLC Staging and Prognostic Factors Committee and of the Advisory Boards, and Participating Institutions. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groups in the Forthcoming (Ninth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2024;19(7):1007–1027. https://doi.org/10.1016/j.jtho.2024.02.011.
29. Qi C, Li W, Li H, Wen F, Zhou L, Sun X, et al. Benefits of prophylactic cranial irradiation in the MRI era for patients with limited stage small cell lung cancer. Front Oncol. 2022;12:833478. https://doi.org/10.3389/fonc.2022.833478.
30. Chen Y, Wang Y, Ren F, Huang Z, Tan B, Zhao Z, et al. Prophylactic cranial irradiation (PCI) versus active surveillance in patients with limited-stage small cell lung cancer: a retrospective, multicentre study. Respir Res. 2022;23(1):274. https://doi.org/10.1186/s12931-022-02196-2.
31. Held MK, Hansen O, Schytte T, Hansen KH, Bahij R, Nielsen M, et al. Outcomes of prophylactic cranial irradiation in patients with small cell lung cancer in the modern era of baseline magnetic resonance imaging of the brain. Acta Oncol. 2022;61(2):185–92. https://doi.org/10.1080/0284186X.2021.1974553.
32. Pezzi TA, Fang P, Gjyshi O, Feng L, Liu S, Komaki R, et al. Rates of overall survival and intracranial control in the magnetic resonance imaging era for patients with limited-stage small cell lung cancer with and without prophylactic cranial irradiation. JAMA Netw Open. 2020;3(4):e201929. https://doi.org/10.1001/jamanetworkopen.2020.1929.
33. National Comprehensive Cancer Network Guidelines, Small Cell Lung Cancer v.2.2025. http://www.nccn.org/guidelines
34. Daly ME, Ismaila N, Decker RH, Higgins K, Owen D, Saxena A, et al. Radiation therapy for small-cell lung cancer: ASCO guideline endorsement of an ASTRO guideline. J Clin Oncol. 2021;39(8):931–9.
35. Simone CB 2nd, Bogart JA, Cabrera AR, Daly ME, DeNunzio NJ, Detterbeck F, et al. Radiation therapy for small cell lung cancer: an ASTRO clinical practice guideline. Pract Radiat Oncol. 2020;10(3):158–73. https://doi.org/10.1016/j.prro.2020.02.009.
36. Ohno Y, Yoshikawa T, Takenaka D, Koyama H, Aoyagi K, Yui M, et al. Small cell lung cancer staging: prospective comparison of conventional staging tests, FDG PET/CT, whole-body MRI, and coregistered FDG PET/MRI. AJR Am J Roentgenol. 2022;218(5):899–908. https://doi.org/10.2214/AJR.21.26868.
37. Graabak G, Grønberg BH, Killingberg KT, Halvorsen TO. Effect of FDG PET-CT for staging and radiotherapy planning - a comparison of cohorts from two randomized trials of

thoracic radiotherapy in limited-stage SCLC. JTO Clin Res Rep. 2024;5(9):100688. https://doi.org/10.1016/j.jtocrr.2024.100688.
38. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primers. 2021;7(1):3. https://doi.org/10.1038/s41572-020-00235-0.

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