European Review for Medical and Pharmacological Sciences 2024; 28: 1562-1574

Long-term outcomes of intensity-modulated radiotherapy in limited-stage small-cell lung cancer classified according to AJCC 8th tumor node metastasis staging system

S. DURU BIRGI[1], S. OZ[1], Y. BABAYIGIT[1], E.B. KOKSOY[2], A. DEMIRKAZIK[2], S. AKYUREK[1]

[1]Department of Radiation Oncology, Ankara University School of Medicine, Ankara, Turkey
[2]Department of Medical Oncology, Ankara University School of Medicine, Ankara, Turkey

Abstract. – OBJECTIVE: The objective of this study was to assess treatment outcomes of intensity-modulated radiotherapy with concomitant chemotherapy and to identify prognostic factors on survival in patients with limited-stage small-cell lung cancer.

PATIENTS AND METHODS: A retrospective analysis was conducted on a cohort of seventy-two patients who received curative treatment between December 2011 and January 2023. Several clinical and biochemical parameters were examined as potential prognostic factors.

RESULTS: The median age was 63 years, and 79% of them were males. Concomitant chemotherapy was administered in 83% of patients. Prophylactic cranial irradiation was applied in 61% of the cohort. Two and five-year overall survival (OS), disease-free survival (DFS), and local relapse-free survival (LRFS) rates were 50% and 25%, 38% and 24%, and 44% and 25%, respectively. Univariate analysis revealed that older age, comorbid lung disease, advanced tumor-node-metastasis (TNM) stage, radiotherapy (RT) alone, and the absence of prophylactic cranial irradiation (PCI) were adverse factors affecting OS. The advanced TNM stage emerged as a significant prognostic factor for LRFS and DFS, with a notable trend toward affecting OS.

CONCLUSIONS: The TNM staging system is of significance in cases classified as limited-stage small-cell lung cancer due to its prognostic implications. Our results suggest that patients with more advanced TNM stage exhibit less favorable treatment outcomes, which may require individual tailoring of new systemic therapies.

Key Words:
Small-cell lung cancer, Tumor staging, Chemoradiotherapy, Radiotherapy, Intensity-modulated radiotherapy.

Introduction

Lung cancer is one of the leading causes of morbidity in the realm of cancer, with small-cell lung cancer (SCLC) comprising approximately 15% of all cases[1]. A significant portion of patients typically receive the diagnosis beyond the limited stage. Historically, the Veterans Affairs (VA) Lung Study Group[2] has employed a two-stage classification system to delineate the extent of disease in patients diagnosed with SCLC. In this scheme: 1- Limited-stage disease is defined as the disease confined solely to the ipsilateral hemithorax, an area amenable to safe radiation field encompassment. It typically includes contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy[3-5]. 2- Extensive-stage disease encompasses disease that extends beyond the ipsilateral hemithorax, which may include malignant pleural or pericardial effusion or hematogenous metastases.

In 2017, the American Joint Committee on Cancer (AJCC) revised the tumor-node-metastasis (TNM) staging system for lung cancer (8th edition) to accommodate SCLC[6-8]. According to this revision, SCLC is categorized into two stages: Limited-stage SCLC (Stage I-III) encompasses cases that can be safely managed with definitive radiation doses, excluding cases where multiple lung nodules are too extensive or possess a tumor/nodal volume that exceeds manageable radiation planning. Extensive-stage SCLC (Stage IV) includes cases where the disease has progressed extensively, typically denoted by distant metastases or extensive tumor/nodal volumes that preclude manageable radiation treatment. Recent-

Corresponding Author: Sumerya Duru Birgi, MD; e-mail: sumeryaduru03@hotmail.com; sdbirgi@ankara.edu.tr

ly, the National Comprehensive Cancer Network (NCCN) SCLC Panel has adopted a combined staging approach that incorporates both the AJCC TNM staging system and the longstanding VA scheme for SCLC. This integrated approach aids in the comprehensive staging of SCLC patients for appropriate treatment planning[3,4,9].

While a few months of survival can be anticipated in untreated patients diagnosed with LS-SCLC, treatment outcomes for this condition, which is recognized for its high sensitivity to chemoradiotherapy (CRT), exhibit significant variability depending on the extent of the disease. The standard treatment approach for patients with limited-stage small-cell lung cancer (LS-SCLC) typically involves a combination of concomitant CRT followed by prophylactic cranial irradiation (PCI) for patients who have responded positively to the initial therapy[10]. This treatment strategy aims to maximize the chances of local and systemic disease control while minimizing the risk of brain metastases, which are a common concern in SCLC. Concomitant CRT, which combines chemotherapy (CT) and radiotherapy (RT) delivered concurrently, is effective in treating the primary tumor and any regional lymph node involvement. This approach has been shown[11,12] to improve both local control and overall survival (OS) in LS-SCLC patients. Following the completion of CRT, PCI is recommended for patients who have demonstrated a favorable response to the initial treatment[13]. By targeting micro metastases that may be present in the brain but are not yet detectable by imaging, PCI can help prolong disease-free survival (DFS) and reduce the incidence of symptomatic brain metastases. Overall, the combination of concomitant CRT and subsequent PCI is guided by a substantial body of clinical evidence demonstrating its efficacy in improving treatment outcomes[14,15]. The standard RT regimen often employs accelerated hyperfractionation. However, conventional fractionation still remains an acceptable option due to the absence of demonstrable inferiority[10,16]. In recent years, advancements in RT techniques have led to the widespread use of intensity-modulated radiotherapy (IMRT) in the treatment of various tumors, including SCLC. IMRT is the preferred method over 3D-conformal external-beam RT (EBRT) due to its reduced toxicity profile. In some instances, more advanced technologies are also considered to minimize normal tissue toxicity, such as 4D-CT, for improved targeting precision[9]. Although some patients achieve complete responses following treatment, a majority of them experience local or distant recurrence, prompting the exploration of factors associated with prognosis. Numerous predictive factors related to patient or disease characteristics impacting survival endpoints have been identified in previous studies[12,14,15,17-28]. These prognostic markers include age, gender, performance status (PS), tumor stage, the timing of RT, and the use of PCI. Furthermore, alongside patient- and treatment-related factors, several routine laboratory tests have shown associations with survival, encompassing lactate dehydrogenase (LDH), C-reactive protein (CRP), albumin, sodium, creatinine, and bilirubin levels[29,30]. Additionally, these biochemical factors can be incorporated into prognostic scores such as the Lung Immune Prognostic Index (LIPI) and Modified Glasgow Prognostic Score (mGPS), which have demonstrated predictive value for survival in SCLC, similar to their utility in other solid tumors[31-34].

In this study, we aimed to evaluate survival outcomes and identify the impact of TNM stage as well as other potential prognostic factors on survival in limited-stage SCLC patients who underwent definitive CRT utilized with IMRT under current advanced conditions.

Patients and Methods

Study Design and Patient Characteristics

We retrospectively evaluated the patients diagnosed with LS-SCLC who underwent definitive CRT at our RT Department between January 2011 and December 2023. Our inclusion criteria encompassed patients who were aged ≥18 years, had a confirmed pathological diagnosis of SCLC, underwent definitive CRT, and had Eastern Cooperative Oncology Group (ECOG) PS of 0-2. We specifically considered patients who received treatment with IMRT. Patients with evidence of metastasis or those diagnosed with extensive-stage SCLC, as well as individuals unable to complete RT, were excluded from this study. The staging of patients adhered to the criteria outlined by the VA Lung Study Group, with additional TNM Staging information recorded under the 8th edition of AJCC Classification as recommended in NCCN guidelines[10]. Demographic information, clinical details, and laboratory data of the patients were retrieved from both patient archive files and the electronic medical records system. Each

patient was clinically staged using chest/abdomen/pelvis computed tomography scans with intravenous contrast and/or fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) before initiating treatment. Additionally, all patients underwent brain magnetic resonance imaging (MRI) at the time of diagnosis to rule out the presence of brain metastasis. This study received ethical approval from our hospital's Ethics Committee, and all participating patients provided informed consent before commencing treatment.

Treatment Characteristics

Treatment for the patients involved a CT regimen consisting of cisplatin (at a dose of 35 mg/m^2) and etoposide (at a dose of 100 mg/m^2), administered every 3 weeks for a total of 4-6 cycles. Thoracic RT was administered concomitantly, typically starting with the second or third cycle of CT. Tumor responses were identified as complete response (CR), partial response (PR), or no response (NR) before the beginning of thoracic RT[35]. In the last four years, four-dimensional computed tomography (4D-CT) was performed during simulation and the average phase of breathing was utilized to delineate both target volume and organs at risk. Before delineation, PET-CT fusion with simulation CT scans were obtained. Thoracic RT encompassed the post-treatment gross tumor volume (GTV) and pretreatment lymph node involvement with a 5 mm margin to the clinical target volume (CTV) and an additional 5-7 mm margin to the planning target volume (PTV). All patients underwent treatment through 5-9 fields IMRT using 6 MV photon energy. RT was delivered in fractions of 2 Gy each, with a total dose of 60-66 Gy. Prophylactic cranial irradiation was administered upon completion of all treatments, with response evaluation performed using chest/whole abdomen/pelvis CT scans and brain MRI to exclude the possibility of brain metastasis. The PCI dose was delivered in 2.5 Gy fraction dose, a total of 10 fractions. In the last 3 years, the patients received hippocampal-sparing brain RT with or without memantine drugs.

Follow-Up

All patients underwent follow-up assessments, including chest/abdomen/pelvis CT scans every 3-4 months during the first 2 years, every 6 months for the subsequent 3 years, and then annually. Brain magnetic resonance imaging (MRI) with contrast, the preferred imaging modality, was conducted at intervals of every 3 to 4 months during the initial year and every 6 months throughout the second year for all patients. Further MRI scans were scheduled as clinically indicated, irrespective of the patient's prophylactic cranial irradiation (PCI) status. Throughout the treatment and follow-up period, any treatment-related acute or late toxicities were documented and categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[36].

Statistical Analysis

SPSS version 25.0 Statistical Software (IBM Corp., Armonk, NY, USA) was used for all analyses. The survival outcomes of the patients and prognostic factors associated with both the patients and their treatment were assessed through Kaplan-Meier survival analysis and Cox regression analysis. The overall survival analysis was carried out from the date of diagnosis until the time of death. Local recurrence-free survival was analyzed from the date of diagnosis until the occurrence of any local event, and disease-free survival was analyzed from the date of diagnosis until the occurrence of any local or distant event or death, whichever transpired first. The impact of various clinical parameters on survival outcomes, such as age, gender, ECOG PS, smoking, chronic obstructive pulmonary disease (COPD), tumor stage, the timing of RT, RT dose, concomitant CT, and PCI, as well as certain biochemical factors including lactate dehydrogenase (LDH), albumin, C-reactive protein (CRP), lung immune prognostic index (LIPI) score, and modified Glasgow Prognostic Score (mGPS), were thoroughly investigated. The lung immune prognostic index score and mGPS were computed using specific biomarkers, namely pre-treatment neutrophil-lymphocyte ratio (dNLR) and serum LDH levels for LIPI, and serum albumin and CRP levels for mGPS. The defined cut-off values were as follows: dNLR at 3 or higher, serum albumin below 3.5 g/dL, CRP at 10 mg/L or above, and the upper limit of the laboratory reference range for serum LDH. The LIPI score was categorized into three groups: "well", "moderate", and "poor", whereas the mGPS was stratified into scores of 0, 1, or 2. Variables with p-values lower than 0.15 in the univariate analysis were subsequently utilized in the Cox regression analysis. The values of $p \leq 0.05$, indicated statistical significance.

Results

In our retrospective analysis, we examined a cohort of 72 patients with LS-SCLC who were treated with CRT utilized with IMRT at our institution. The median age of the patients was 63 years (range 46-83 years). Among the patients' cohort, 79% (n=57) were males. The ECOG PS was 0-1 in 92% (n=66) of the patients. Additional comorbidities were present in 65% (n=47) of the patients, with the most common comorbidity being COPD, existing in 30% (n=14) of the cases. The majority (92%) of patients had stage III disease at the time of diagnosis. An overview of patient, tumor, and treatment characteristics is provided in Table I.

Patients received a median of 6 cycles of total CT during their primary treatment, ranging from 2 to 6 cycles, with 78% of them undergoing the cisplatin-etoposide scheme. Before commencing RT, 85% (n=61) of patients exhibited a complete (13%) or partial response (72%) to CT. 4D-CT simulation was performed in nearly half of the patients (n=35, 49%). All patients were treated with a median 7-field IMRT. The median total RT dose was 60 Gy (range 50-66 Gy), in once-daily 2 Gy fractions. Concomitant CT with RT was carried out in 83% (n=60) of patients. Radiotherapy was commenced at the median of the third cycle (with a range of 1 to 5) of CT, while a median of 2 cycles (with a range of 1 to 3) of CT were concurrently administered

Table I. Patient and treatment-related characteristics of the patient cohort.

Features	Number (ratio)
Age (y)	Median 63 y (range: 46-83 y)
≥ 70	16 (22%)
< 70	56 (78%)
Gender	
Female	15 (21%)
Male	57 (79%)
ECOG Performance	
0	7 (10%)
1	59 (82%)
2	6 (8%)
Smoking	
Current	42 (58%)
Never	3 (4%)
Former	26 (37%)
Comorbidity Type	
COPD	14 (20%)
Others	33 (45%)
No	25 (35%)
Tumor stage	
T1	10 (14%)
T2	16 (22%)
T3	16 (22%)
T4	30 (42%)
Node stage	
N0	3 (4%)
N1	6 (8%)
N2	38 (53%)
N3	25 (35%)
Stage (AJCC 8th Ed.)	
I	1 (1%)
II	5 (7%)
IIIA	14 (20%)
IIIB	34 (47%)
IIIC	18 (25%)

Features	Number (ratio)
Total CT cycles	6 (2-6)
CT type	
Cisplatin-etoposide	56 (78%)
Carboplatin-etoposide	13 (18%)
RT dose	
> 60 Gy	18 (25%)
≤ 60 Gy	54 (75%)
Pre-RT CT response	
Complete	9 (12%)
Partially	52 (73%)
Stable	5 (7%)
Progression	2 (3%)
Conc CT with RT	
Yes	60 (83%)
No	12 (17%)
Conc CT cycles with RT	2 (1-3)
CT cycle before RT	3 (1-5)
PCI	
Yes	44 (61%)
No	28 (39%)
Cranial imaging pre-PCI	
MRI	33 (75%)
Computed Tomograpy	9 (20%)
No imaging	2 (5%)
LIPI score	
Well	34 (48%)
Moderate	30 (43%)
Poor	6 (9%)
mGPS	
0	33 (47%)
1	34 (49%)
2	3 (4%)

y: years, ECOG: Eastern Cooperative Oncology Group, COPD: Chronic Obstructive Pulmonary Disease, CT: Chemotherapy, RT: radiotherapy, Gy: Gray, AJCC 8th Ed.: The Eighth Edition of American Joint Committee on Cancer Staging, NLR: neutrophil-lymphocyte ratio, LIPI: Lung Immune Prognostic Index, mGPS: Modified Glasgow Prognostic Score, Conc: concomitant, PCI: prophylactic cranial irradiation, MRI: Magnetic resonance imaging, Gy: Gray.

Table II. Univariate log-rank analysis results of the patient, disease and treatment related factors affecting overall survival (OS), local relapse-free (LRFS), and disease-free survival (DFS).

Factors	OS *p*-value	LRFS *p*-value	DFS *p*-value
Age ≥ 70 *vs.* < 70	0.003	0.01	0.02
Gender	0.97	0.861	0.245
Smoking	0.5	0.458	0.574
ECOG (0-1 *vs.* 2)	0.86	0.793	0.894
COPD	0.012	0.001	0.007
Tumor stage	0.147	0.164	0.599
Node stage	0.338	0.492	0.508
Stage > IIIA *vs.* ≤ IIIA	0.057	0.04	0.06
Response to CT (no resp *vs.* comp-part)	0.001	0.041	0.029
Biochemical Factors			
NLR	0.956	0.725	0.729
Serum LDH	0.271	0.196	0.678
LIPI score	0.286	0.426	0.760
Serum albumin	0.483	0.775	0.678
Serum CRP	0.984	0.626	0.465
mGPS	0.746	0.331	0.388
Treatment-related Factors			
CT total cycle (≤ 4 *vs.* > 4)	0.876	0.712	0.524
RT dose (> 60 Gy *vs.* ≤ 60 Gy)	0.608	0.698	0.474
Conc CT with RT (Yes *vs.* No)	0.022	0.03	0.024
Conc CT cycle with RT	0.246	0.184	0.373
CT cycle before CRT ≤ 2 *vs.* > 2	0.950	0.215	0.299
PCI (Yes *vs.* No)	< 0.001	0.0001	0.0001

OS: Overall Survival, LRFS: Local relapse-free survival, DFS: Disease-free survival, ECOG: Eastern Cooperative Oncology Group, COPD: Chronic Obstructive Pulmonary Disease, CT: Chemotherapy, NLR: neutrophil-lymphocyte ratio, LIPI: Lung Immune Prognostic Index, mGPS: Modified Glasgow Prognostic Score, Conc: concomitant, PCI: prophylactic cranial irradiation, CRT: chemoradiotherapy, Gy: Gray.

during RT. Sixty-one percent (n=44) of patients had PCI after thoracic treatment. Notably, brain assessment using MRI was conducted in 95% (n=42) of patients before initiating PCI. As for pretreatment biochemical factors, the LIPI score was categorized as follows: 48% "well", 43% "moderate", and 9% "poor", respectively. The modified Glasgow Prognostic Score (mGPS) was distributed as follows: 47% had a score of 0, 49% had a score of 1, and 4% had a score of 2.

At a median follow-up duration of 16 months (range 3-97 months), the median survival was 24 months, accompanied by corresponding two and five-year OS rates of 50% and 25%, respectively. Additionally, we observed median survival periods for DFS and local relapse-free survival (LRFS) to be 18 and 22 months, with corresponding two and five-year survival rates of 38% and 24%, 44%, and 25%, respectively (Table II) (Figures 1-3).

In our univariate analysis, several negatively prognostic factors for all survival endpoints emerged as age ≥70 years, COPD, advanced TNM stage (>IIIA), no response to CT, RT without concomitant CT, and the omission of PCI. Conversely, no significant correlation

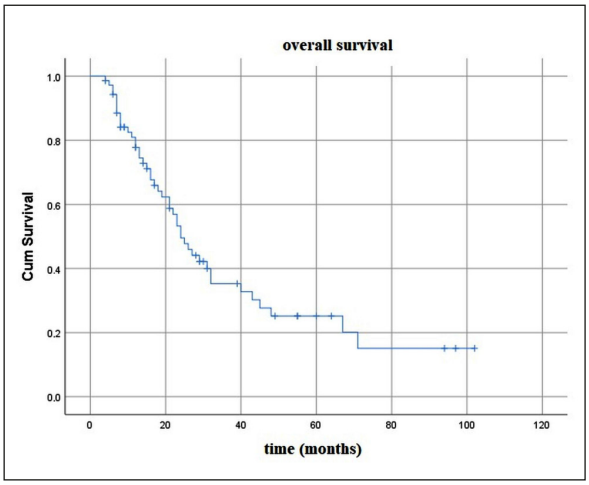

Figure 1. Kaplan-Meier analysis results for overall survival.

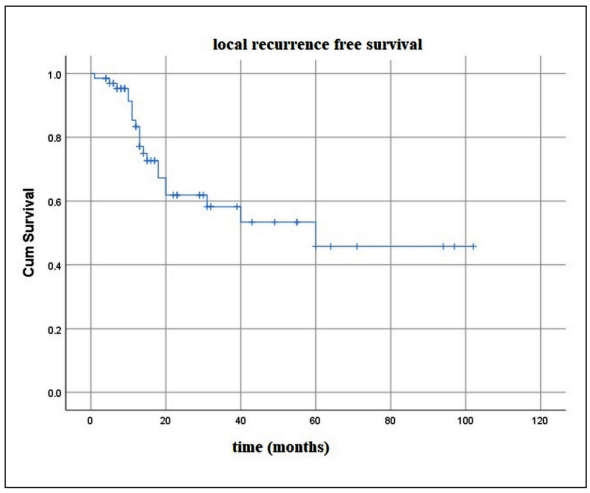

Figure 2. Kaplan-Meier analysis results for local recurrence-free survival.

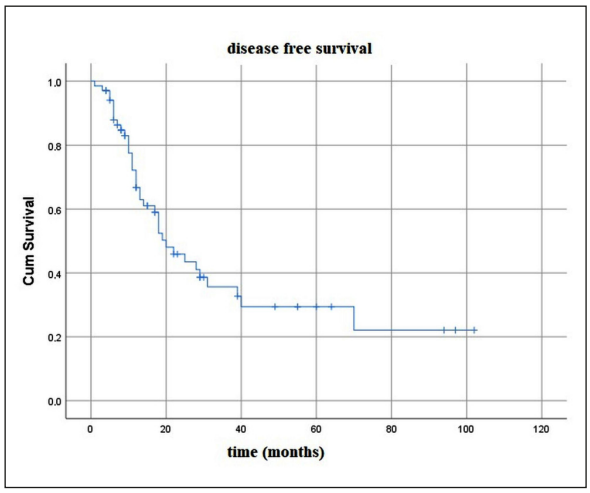

Figure 3. Kaplan-Meier analysis results for disease-free survival.

was identified between biochemical markers and survival outcomes. However, in our multivariate analysis, it is noteworthy that, among all factors considered, none were identified as significant prognostic factors except a negative trend of advanced TNM stage for OS. The advanced TNM stage played a prominent role in LRFS and DFS, while COPD emerged as a significant factor in reducing local control rates (Table III) (Figures 4-6).

Regarding acute toxicity, grade 3-4 hematologic toxicity was observed in 17% (n=12) of patients. These adverse events were neutropenia, thrombocytopenia and anemia. Nonetheless, acute non-hematologic toxicity constituted only 7% (n=5) of the patient cohorts distributed as grade 3 esophagitis in 2 and grade 3 pneumonitis in 3 patients. No acute grade 4 or more non-hematologic toxicity had been observed. Additionally, during follow-up, no grade 4 or higher late hematologic, esophageal, or pulmonary toxicities were observed in any of the patients.

Discussion

In the case of limited-stage SCLC, the standard treatment approach involves concomitant CRT and PCI for responding patients. Despite these treatment modalities, the expected median survival is around 23 months[10]. In

Table III. Multivariate analysis results of the patient, disease and treatment related prognostic factors affecting overall Survival (OS), local relapse-free survival (LRFS), and disease-free survival (DFS).

Factors	OS		LRFS		DFS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age ≥ 70 y *vs.* < 70 y	0.48 (0.19-1.22)	0.12	1.4 (0.5-3.7)	0.48	1.4 (0.6-3.5)	0.46
COPD disease Yes *vs.* No	1.96 (0.81-4.7)	0.13	3.2 (1.1-9)	**0.02**	2.1 (0.8-5.1)	0.09
Stage ≤ IIIA *vs.* > IIIA	2.99 (0.85-10.4)	**0.08**	3.5 (0.9-12)	**0.05**	3.8 (1-13.2)	**0.03**
Response to CT (comp-part *vs.* no resp)	0.98 (0.19-5)	0.98	0.91 (0.15-5)	0.92	0.6 (0.1-3.1)	0.54
Conc CT with RT (Yes *vs.* No)	2.46 (0.64-9.3)	0.18	2.3 (0.48-11)	0.28	2.6 (0.6-10)	0.17
PCI (Yes *vs.* No)	0.28 (0.64- 4.3)	0.28	1.1 (0.4-3.4)	0.79	1.3 (0.5-3.5)	0.58

y: years, OS: Overall Survival, LRFS: Local relapse-free survival, DFS: Disease-free survival, COPD: Chronic Obstructive Pulmonary Disease, CT: Chemotherapy, Conc: concomitant, PCI: prophylactic cranial irradiation, comp: complete, part: partially, resp: response.

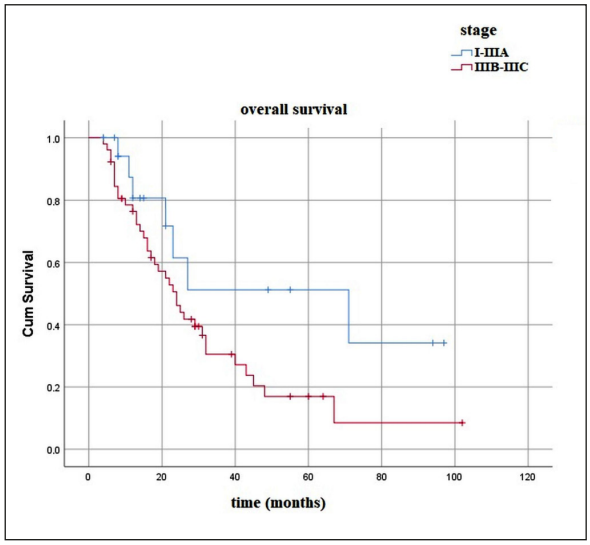

Figure 4. Overall survival curve by stage.

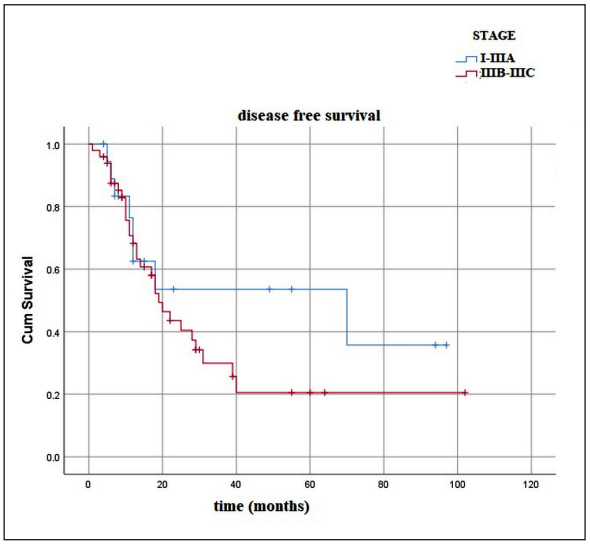

Figure 6. Disease-free survival curve by stage.

this retrospective study, our long-term results unveiled a median OS of 24 months, with corresponding two- and five-year OS rates of 50% and 25%. The two and five-year DFS and LRFS rates were observed to be 38% and 24%, and 44% and 25%, respectively. The advanced TNM stage (>IIIA) has emerged as a prominent prognostic factor for both LRFS and DFS, displaying a notable trend toward influencing OS. Additionally, COPD has been identified as a significant factor contributing to a reduction in local control rates.

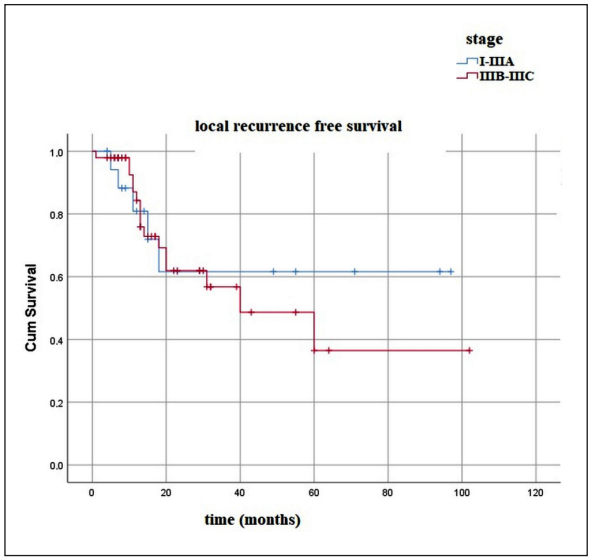

Figure 5. Local recurrence-free survival curve by stage.

In the treatment of LS-SCLC, thoracic radiation therapy combined with etoposide/cisplatin chemotherapy results in response rates ranging from 70% to 90%. Patients also experience a median overall survival of 25 to 30 months, with 5-year overall survival rates ranging from 31% to 34%[16]. The application of thoracic RT contributes to a 25% enhancement in local control rates among patients afflicted with limited-stage disease, concurrently associated with improved survival[11,12].

For patients diagnosed with LS-SCLC and undergoing treatment with CRT and PCI, Turrisi et al[10] reported a median survival time of 23 months, along with two and five-year survival rates of 47% and 26%, respectively. They achieved improved survival outcomes with a twice-daily treatment regimen, which subsequently became the accepted standard approach for LS-SCLC. Nevertheless, owing to the challenges linked to implementing a twice-daily regimen in clinical practice and apprehensions regarding the potential for improved local control with higher RT doses, the subsequent CONVERT trial[16] achieved a median OS of 30 months. The two- and five-year OS rates stood at 56% and 34% with the twice-daily regimen, respectively, and no statistically significant differences were obtained when compared to the once-daily high-dose regimen[16]. Moreover, another recently published Phase III randomized trial[37], CALGB 30610 (Alliance)/RTOG 0538, aimed to establish the superiority of dose esca-

lation to a 70 Gy once-daily regimen over a 45 Gy twice-daily regimen but could not demonstrate such superiority. In our study, the survival outcomes were consistent with the existing literature, even when utilizing a once-daily treatment regimen with a median of 60 Gy doses. Additionally, our LRFS outcomes, with a median duration of 22 months, were in line with the results of the CONVERT trial[16]. Notably, our analysis did not reveal any significant benefits from dose escalation beyond 60 Gy in terms of survival outcomes, in accordance with previously published phase III trials[37].

Prophylactic cranial irradiation is considered the standard of care for LS-SCLC patients who have exhibited a positive response to initial CRT, as supported by two meta-analyses[14,15]. Aupérin et al[14] conducted a meta-analysis indicating a 5% OS advantage for SCLC patients in complete remission who received PCI. Subsequently, in 2001, Meert et al[15] conducted a review and meta-analysis, corroborating the survival advantage associated with PCI. However, it is worth noting that brain imaging with brain CT was only conducted in two of the trials[14,15], raising concerns about whether PCI might function as therapy in cases with subclinical brain metastasis. A recent meta-analysis[38] from China, focusing on the era of pretreatment brain MRI, confirmed that PCI still offers a survival advantage. However, it is important to note that the included studies lacked MRI surveillance in the no PCI groups, making it unclear how PCI compares to the strategy of no PCI with MRI observation. The ongoing trials related to this matter will provide further guidance. In our study, the univariate analysis demonstrated that PCI contributes to both OS and DFS, aligning with the findings of these previous trials[14,15,38]. However, in the multivariate analysis, no statistically significant relationship was observed, probably because nearly all patients were assessed using brain MRI with evidence of no metastatic findings before PCI.

In prior investigations[22-24], several significant negative prognostic factors were identified, including advanced stage, older age, male gender, and a performance status (PS) of 3-4, impacting survival. Among these factors, the stage stands out as the most pivotal prognostic determinant[27]. While SCLC has historically been staged in accordance with the VA classification, it is noteworthy that the TNM classification also has shown[39] prognostic significance for survival. Moreover, a direct correlation between both the T and N stages and survival has been empirically demonstrated in previous literature[26]. In our study, 92% of the patients were at stage III according to AJCC 8th TNM classification. Our analysis revealed that stage IIIB and higher disease stages had a negative impact on LRFS and DFS, as determined by multivariate analyses. There is also a decreasing trend in OS. However, the T and N stages separately were not statistically significant on any survival outcomes.

In our study, older age (≥70 years) was associated with lower OS, LRFS, and DFS rates, as demonstrated in our univariate analyses; however, these results were not proved significant in multivariate analysis because only 22% of the patients in this study were over 70 years old. Gaspar et al[21] reported that older age and male gender were associated with a higher risk of mortality. Turrisi et al[10] also reported that the male gender and a performance status of 2 were associated with worse failure-free survival. A SEER data analysis similarly found that male sex and older age were associated with a higher risk of mortality[25]. However, in our study, we did not find any disadvantage associated with older age, gender, or performance status in terms of OS or DFS, likely due to the relatively small number of patients in the study.

SCLC is a smoking-related disease, and in our study, only 4% of patients were never smokers, consistent with previous reports[1,16,40]. In some studies[40,41], the authors have reported conflicting results about smoking status and survival outcomes. We found no impact of smoking status on OS, LRFS, or DFS. Chronic obstructive pulmonary disease (COPD) is another issue, known to increase the risk of lung cancer. However, the prognostic effect of COPD on lung cancer outcomes remains unclear[42]. Some previously reported studies[43,44] did not find any prognostic effect on OS or progression-free survival for SCLC patients, while others[45] found a negative impact on OS for NSCLC patients. In our analysis, coexisting COPD was associated with a negative effect on LRFS with statistical significance in SCLC patients.

Regarding treatment-related factors, we have confirmed the failure to administer concomitant CT (CC CT) alongside RT emerged as a negative predictor of OS, as determined by the

log-rank test. The current guidelines for SCLC strongly recommend CC CRT for patients who exhibit good performance levels, backed by robust evidence[46]. For patients with LS-SCLC, it is recommended to undergo early CC CRT based on evidence from previous trials[27,47-49]. For instance, a phase III trial[50] conducted by the Japanese Cooperative Oncology Group compared sequential *vs.* concomitant thoracic RT combined with etoposide/cisplatin in 231 patients with limited-stage disease. The results indicated that OS was 27.2 months for those receiving CC CRT, compared to 19.7 months for those receiving sequential CRT (p=.097). It is noteworthy that patients undergoing concomitant CRT did experience more severe hematologic toxicity, and severe esophagitis occurred in 9% of these patients compared to 4% in the sequential CRT group. The timing of thoracic RT, specifically early *vs.* late initiation, has been a subject of assessment and is believed to have potential contributions to survival. The prevailing recommendation is to commence RT during the first or second cycle of CT. A randomized phase III trial[51] conducted by the National Cancer Institute of Canada compared the initiation of RT at either cycle 2 or cycle 6 of CT. This trial showed that early RT was associated with improved local and systemic disease control, as well as longer survival. Several systematic reviews and meta-analyses[48,49] examining the timing of thoracic RT in LS-SCLC have consistently indicated that early CC CRT leads to a modest yet significant improvement in OS when compared to late concomitant or sequential CRT. Another meta-analysis[27] focused on limited-stage SCLC patients demonstrated that survival was enhanced with a more expeditious completion of the CRT regimen, covering the period from the commencement of any CT until the conclusion of RT. However, it is important to note that early concomitant CRT was associated with an increase in severe acute esophagitis compared to the late concomitant approach in a meta-analysis[47] of individual patient data from 12 trials comprising 2,668 patients. This signifies the need for careful consideration of treatment-related toxicities when determining the optimal treatment strategy for each patient. Our study did not reveal a clear benefit associated with early RT. This discrepancy may be attributed to variations in CT compliance among the patients included in our study. Furthermore, in our center, the standard CT practice is administering four to six cycles of cisplatin-etoposide if the patient exhibits a good performance status (PS). However, our analysis did not identify any benefit derived from administering more than four courses of CT, a finding that aligns with historical data from a randomized study[52].

In addition to patient- and treatment-related factors, several standard laboratory tests have been linked to survival, encompassing LDH, CRP, albumin, sodium, creatinine, and bilirubin. Additionally, the literature[31-34] shows a growing body of evidence supporting the prognostic significance of NLR, LIPI score, and mGPS for SCLC and other solid tumors. For instance, Sun et al[31] conducted a retrospective study involving 497 patients with LS-SCLC and found that the LIPI score was a prognostic factor for both OS and PFS. In our study, we assessed biochemical prognostic factors such as the LIPI score, mGPS, and individual components like serum albumin, CRP, LDH, and NLR. However, we did not observe any impact of these factors on OS and DFS. The lack of significant findings in our study for these biochemical factors may indeed be attributed to the relatively small number of patients included.

Regarding toxicity, comparable results have been reported in previous studies[10,16,37]. Turrisi et al[10] observed a 16% incidence of grade 3 or higher esophagitis in the once-daily (QD) arm and a 32% incidence in the twice-daily (BID) arm. In the CALGB study[37], grade 3 or higher esophagitis rates were 16% and 17.5% in the 45 Gy and 70 Gy groups, respectively. In the CONVERT trial[16], although toxicity profiles were generally similar between the treatment arms, patients receiving accelerated 45 Gy had a higher incidence of Grade 4 neutropenia compared to those receiving conventional 66 Gy (49% *vs.* 38%; p=.05). Grade 3 or higher esophagitis rates were similar with 18-19% rates. Overall, higher doses were associated with an increased occurrence of grade 5 adverse events in both the CALGB and CONVERT trials[16,37]. A randomized phase II trial[53] compared high-dose (65 Gy/5 weeks) accelerated RT with standard-dose (45 Gy/3 weeks) accelerated RT, and no survival advantage was observed. However, the toxicity profiles in this trial were as follows: 17.4% for grade 3 or higher esophagitis rates *vs.* 15.3% for standard-dose; grade 3 or higher pneumonitis rates were 3.3% for the high-dose

vs. 2.4% for standard-dose and treatment-related deaths were comparable between the two groups (high-dose: 2.2% *vs*. standard-dose: 1.2%). Regarding adverse events in our study, we observed lower toxicity rates of 3% grade 3 esophagitis and 4% grade 3 pneumonitis. Additionally, no grade 5 adverse events were experienced in our study. Treatment using IMRT in all patients, as well as the use of 4D-CT simulation in nearly half of the patients, may contribute to this favoring toxicity outcome by enhancing effective targeting while protecting organs at risk.

Limitations

The limitations of this study are its retrospective design, a small number of patient cohorts, and heterogeneity in CT course, schedules, as well as RT timing and doses. Prognostic factors can vary widely depending on the study population and the size of the cohort. Larger sample sizes and more comprehensive data may be needed to detect significant associations between patient, treatment, or biochemical factors and survival outcomes.

Conclusions

The VA classification system, which has been in use for many decades in SCLC, is characterized by its broad and heterogeneous nature. Unfortunately, this classification system struggles to accurately identify subgroups that may have a significant impact on treatment decisions and prognosis. Efforts have been made to assess the suitability of the TNM classification system for SCLC, but most studies[54,55] have primarily focused on small cohorts with a bias toward surgical cases. However, it is important to recognize that in SCLC, the majority of patients are categorized using clinical staging (cTNM), primarily relying on imaging modalities such as CT scans, PET-CT scans, and MRI scans. The analysis of tumor size, as incorporated into the 8th edition of the TNM staging system, has provided valuable insights into the potential for further subclassification of tumors based on their size. As we continue to refine our understanding of SCLC, these findings underscore the importance of adopting a more precise and clinically relevant staging system that can better guide treatment decisions and improve prognostic accuracy for this challenging disease.

In conclusion, despite the utilization of state-of-the-art RT techniques and standard systemic treatments, our survival outcomes in LS-SCLC did not attain the desired levels, mirroring the findings in the existing literature. Given the observed heterogeneity beyond this restricted stage, it becomes imperative to stage patients according to the AJCC TNM classification. Furthermore, there is a pressing need for further prospective trials to assess the potential effectiveness of various systemic or targeted agents' contribution in the more advanced stages within the limited-stage disease category, with the ultimate aim of improving patient outcomes.

Conflict of Interest

The authors declare that they have no conflicts of interest to report regarding the present study.

Authors' Contribution

All authors reviewed the results and approved the final version of the manuscript. Conceptualization, S.D.B and Y.B.; Methodology, S.A.; Software, E.B.K.; Validation, S.D.B., S.Ö and A.D.; Formal Analysis, E.B.K; Investigation, Y.B., S.Ö; Resources, S.A.; Data Curation, S.Ö.; Writing – Original Draft Preparation, S.D.B.; Writing – Review and Editing, S.A.; Visualization, E.B.K.; Supervision, A.D.; Project Administration, A.D.

ORCID ID

Sumerya Duru Birgi: 0000-0003-4260-1018
Sumeyra Oz: 0000-0003-0203-5816
Yunus Babayigit: 0009-0003-7854-1560
Elif Berna Koksoy: 0000-0002-6590-4444
Ahmet Demirkazik: 0000-0002-2917-7999
Serap Akyurek: 0000-0001-8840-0233

Funding

The authors received no specific funding for this study.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Ankara University (protocol code: I07-503-23, August 21, 2023).

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Data Availability

The data presented in this study are available on request from the corresponding author.

References

1) Basumallik N, Agarwal M. Small Cell Lung Cancer. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
2) Micke P, Faldum A, Metz T, Beeh KM, Bittinger F, Hengstler JG, Buhl R. 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: 271-276.
3) Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143: 400-419.
4) Kalemkerian GP, Gadgeel SM. Modern staging of small cell lung cancer. J Natl Compr Canc Netw 2013; 11: 99-104.
5) Kalemkerian GP. Staging and imaging of small cell lung cancer. Cancer Imaging 2012; 11: 253-258.
6) Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, et al. (Eds.). AJCC Cancer Staging Manual (8th edition). Springer International Publishing: American Joint Commission on Cancer; 2017.
7) 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: 300-311.
8) Rami-Porta R, Bolejack V, Giroux DJ, Chansky K, Crowley J, Asamura H, Goldstraw P. International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Board Members and Participating Institutions. The IASLC lung cancer staging project: the new database to inform the eighth edition of the TNM classification of lung cancer. J Thorac Oncol 2014; 9: 1618-1624.
9) Ganti AKP, Loo BW, Bassetti M, Blakely C, Chiang A, D'Amico TA, D'Avella C, Dowlati A, Downey RJ, Edelman M, Florsheim C, Gold KA, Goldman JW, Grecula JC, Hann C, Iams W, Iyengar P, Kelly K, Khalil M, Koczywas M, Merritt RE, Mohindra N, Molina J, Moran C, Pokharel S, Puri S, Qin A, Rusthoven C, Sands J, Santana-Davila R, Shafique M, Waqar SN, Gregory KM, Hughes M. Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021; 19: 1441-1464.
10) Turrisi AT 3rd, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, Wagner H, Aisner S, Johnson DH. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999; 340: 265-271.
11) Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, Brodin O, Joss RA, Kies MS, Lebeau B, Onoshi T, Østerlind K, Tattersall MHN, Wagner H. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992; 327: 1618-1624.
12) Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 1992; 10: 890-895.
13) Yang CF, Chan DY, Speicher PJ, Gulack BC, Wang X, Hartwig MG, Onaitis MW, Tong BC, D'Amico TA, Berry MF, Harpole DH. Role of Adjuvant Therapy in a Population-Based Cohort of Patients With Early-Stage Small-Cell Lung Cancer. J Clin Oncol 2016; 34: 1057-1064.
14) Aupérin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, Kristjansen PE, Johnson BE, Ueoka H, Wagner H, Aisner J. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999; 341: 476-484.
15) Meert AP, Paesmans M, Berghmans T, Martin B, Mascaux C, Vallot F, Verdebout JM, Lafitte JJ, Sculier JP. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer 2001; 1: 5.
16) Faivre-Finn C, Snee M, Ashcroft L, Appel W, Barlesi F, Bhatnagar A, Bezjak A, Cardenal F, Fournel P, Harden S, Le Pechoux C, McMenemin R, Mohammed N, O'Brien M, Pantarotto J, Surmont V, Van Meerbeeck JP, Woll PJ, Lorigan P, Blackhall F; CONVERT Study Team. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol 2017; 18: 1116-1125.
17) Li J, Dai CH, Chen P, Wu JN, Bao QL, Qiu H, Li XQ. Survival and prognostic factors in small cell lung cancer. Med Oncol 2010; 27: 73-81.
18) Aref H, Refaat S. CRP evaluation in non-small cell lung cancer. Egypt J Chest Tuber 2014; 63: 717-722.
19) Kim HJ, Choi CM, Kim SG. The Younger Patients Have More Better Prognosis in Limited Disease Small Cell Lung Cancer. Tuberc Respir Dis 2016; 79: 274-281.
20) Ma X, Zhang Z, Chen X, Zhang J, Nie J, Da L, Hu W, Tian G, Wu D, Han J, Han S, Long J, Wang Y, Fang J. Prognostic factor analysis of patients with small cell lung cancer: Real-world data from 988 patients. Thorac Cancer 2021; 12: 1841-1850.

21) Gaspar LE, McNamara EJ, Gay EG, Putnam JB, Crawford J, Herbst RS, Bonner JA. Small-cell lung cancer: prognostic factors and changing treatment over 15 years. Clin Lung Cancer 2012; 13: 115-122.

22) Foster NR, Mandrekar SJ, Schild SE, Nelson GD, Rowland KM Jr, Deming RL, Kozelsky TF, Marks RS, Jett JR, Adjei AA. Prognostic factors differ by tumor stage for small cell lung cancer: a pooled analysis of North Central Cancer Treatment Group trials. Cancer 2009; 115: 2721-2731.

23) Jackman DM, Johnson BE. Small-cell lung cancer. Lancet 2005; 366: 1385-1396.

24) van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet 2011; 378: 1741-1755.

25) Lally BE, Geiger AM, Urbanic JJ, Butler JM, Wentworth S, Perry MC, Wilson LD, Horton JK, Detterbeck FC, Miller AA, Thomas CR Jr, Blackstock AW. Trends in the outcomes for patients with limited stage small cell lung cancer: An analysis of the Surveillance, Epidemiology, and End Results database. Lung Cancer 2009; 64: 226-231.

26) Shepherd FA, Crowley J, Van Houtte P, Postmus PE, Carney D, Chansky K, Shaikh Z, Goldstraw P; International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. 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: 1067-1077.

27) De Ruysscher D, Pijls-Johannesma M, Vansteenkiste J, Kester A, Rutten I, Lambin P. Systematic review and meta-analysis of randomised, controlled trials of the timing of chest radiotherapy in patients with limited-stage, small-cell lung cancer. Ann Oncol 2006; 17: 543-552.

28) Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, Movsas B, Wasserman T, Rosenthal SA, Gore E, Machtay M, Sause W, Cox JD. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst 2011; 103: 1452-1460.

29) Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. J Clin Oncol 1990; 8: 1563-1574.

30) Shao N, Cai Q. High pretreatment serum C-reactive protein level predicts a poor prognosis for combined small-cell lung cancer. Tumour Biol 2015; 36: 8465-8470.

31) Sun B, Hou Q, Liang Y, Xue S, Yao N, Wei L, Cao X, Li H, Si H, Cao J. Prognostic ability of lung immune prognostic index in limited-stage small cell lung cancer. BMC Cancer 2022; 22: 1233.

32) Wasamoto S, Imai H, Tsuda T, Nagai Y, Minemura H, Yamada Y, Umeda Y, Kishikawa T, Shiono A, Kozu Y, Shiihara J, Yamaguchi O, Mouri A, Kaira K, Kanazawa K, Taniguchi H, Kaburagi T, Minato K, Kagamu H. Pretreatment glasgow prognostic score predicts survival among patients administered first-line atezolizumab plus carboplatin and etoposide for small cell lung cancer. Front Oncol 2023; 12: 1080729.

33) Minami S, Ogata Y, Ihara S, Yamamoto S, Komuta K. Pretreatment Glasgow prognostic score and prognostic nutritional index predict overall survival of patients with advanced small cell lung cancer. Lung Cancer 2017; 8: 249-257.

34) Yang C, Ren G, Yang Q. Prognostic value of preoperative modified Glasgow prognostic score in surgical non-small cell lung cancer: A meta-analysis. Front Surg 2023; 9: 1094973.

35) Jeremic B, Shibamoto Y, Acimovic L, Djuric L. Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer. J Clin Oncol 1995; 13: 452-458.

36) Common Terminology Criteria for Adverse Events (CTCAE) (2010). National Cancer Institute (U.S.) Version 4.0. U.S. Department of Health and Human Service. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Documentation/CTCAE_Governance_2010-03-11.pdf.

37) Bogart J, Wang X, Masters G, Gao J, Komaki R, Gaspar LE, Heymach J, Bonner J, Kuzma C, Waqar S, Petty W, Stinchcombe TE, Bradley JD, Vokes E. High-Dose Once-Daily Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer: CALGB 30610 (Alliance)/RTOG 0538. J Clin Oncol 2023; 41: 2394-2402.

38) Liu J, Shen B, Yang Y, Guo J, Ren W, Zhou Q, Mao J, Ye W, Wu D. Survival benefit of prophylactic cranial irradiation in limited-stage small-cell lung cancer in modern magnetic resonance imaging staging: a systematic review and meta-analysis. Acta Oncol 2023; 62: 305-314.

39) Zhao Z, Gao Y, Tan F, Xue Q, Gao S, He J. Prognostic significance of eighth edition TNM stage criteria in combined small-cell lung cancer. Front Oncol 2023; 13: 1018288.

40) Liu X, Jiang T, Li W, Li X, Zhao C, Shi J, Zhao S, Jia Y, Qiao M, Zhang L, Luo J, Gao G, Zhou F, Wu F, Chen X, He Y, Ren S, Su C, Zhou C. Characterization of never-smoking and its association with clinical outcomes in Chinese patients with small-cell lung cancer. Lung Cancer 2018; 115: 109-115.

41) Tseng JS, Chiang CJ, Chen KC, Zheng ZR, Yang TY, Lee WC, Hsu KH, Huang YH, Liu TW, Hsia JY, Chang GC. Association of Smoking With Patient Characteristics and Outcomes in Small Cell Lung Carcinoma, 2011-2018. JAMA Netw 2022; 5: 224830.

42) Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. Am J Respir Crit Care Med 2007; 176: 285-290.

43) Ju S, Lee HR, Kim JY, Kim HC, Lee GW, You JW, Cho YJ, Jeong YY, Lee JD, Lee SJ. Impact of coexistent chronic obstructive pulmonary disease on the survival of patients with small cell lung cancer receiving chemotherapy. Thorac Cancer 2018; 9: 1271-1278.

44) van de Schans SA, Janssen-Heijnen ML, Biesma B, Smeenk FW, van de Poll-Franse LV, Seynaeve C, Coebergh JW. COPD in cancer patients: higher prevalence in the elderly, a different treatment strategy in case of primary tumours above the diaphragm, and a worse overall survival in the elderly patient. Eur J Cancer 2007; 43: 2194-2202.

45) Zhai R, Yu X, Shafer A, Wain JC, Christiani DC. The impact of coexisting COPD on survival of patients with early-stage non-small cell lung cancer undergoing surgical resection. Chest 2014; 145: 346-353.

46) Simone CB 2nd, Bogart JA, Cabrera AR, Daly ME, DeNunzio NJ, Detterbeck F, Faivre-Finn C, Gatschet N, Gore E, Jabbour SK, Kruser TJ, Schneider BJ, Slotman B, Turrisi A, Wu AJ, Zeng J, Rosenzweig KE. Radiation Therapy for Small Cell Lung Cancer: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2020; 10: 158-173.

47) De Ruysscher D, Lueza B, Le Péchoux C, Johnson DH, O'Brien M, Murray N, Spiro S, Wang X, Takada M, Lebeau B, Blackstock W, Skarlos D, Baas P, Choy H, Price A, Seymour L, Arriagada R, Pignon JP; RTT-SCLC Collaborative Group. Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis. Ann Oncol 2016; 27: 1818-1828.

48) Pijls-Johannesma MC, De Ruysscher D, Lambin P, Rutten I, Vansteenkiste JF. Early versus late chest radiotherapy for limited stage small cell lung cancer. Cochrane Database Syst Rev 2005; 2004: 004700.

49) Fried DB, Morris DE, Poole C, Rosenman JG, Halle JS, Detterbeck FC, Hensing TA, Socinski MA. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 2004; 22: 4837-4845.

50) Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S, Nishiwaki Y, Watanabe K, Noda K, Tamura T, Fukuda H, Saijo N. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 2002; 20: 3054-3060.

51) Murray N, Coy P, Pater JL, Hodson I, Arnold A, Zee BC, Payne D, Kostashuk EC, Evans WK, Dixon P, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1993; 11: 336-344.

52) Veslemes M, Polyzos A, Latsi P, Dimitroulis J, Stamatiadis D, Dardoufas C, Rasidakis A, Katsilambros N, Jordanoglou J. Optimal duration of chemotherapy in small cell lung cancer: a randomized study of 4 versus 6 cycles of cisplatin-etoposide. J Chemother 1998; 10: 136-140.

53) Qiu B, Li Q, Liu J, Huang Y, Pang Q, Zhu Z, Yang X, Wang B, Chen L, Fang J, Lin M, Jiang X, Guo S, Guo J, Wang D, Liu F, Chu C, Huang X, Xie C, Liu H. Moderately Hypofractionated Once-Daily Compared With Twice-Daily Thoracic Radiation Therapy Concurrently With Etoposide and Cisplatin in Limited-Stage Small Cell Lung Cancer: A Multicenter, Phase II, Randomized Trial. Int J Radiat Oncol Biol Phys 2021; 111: 424-435.

54) Byhardt RW, Hartz A, Libnoch JA, Hansen R, Cox JD. Prognostic influence of TNM staging and LDH levels in small cell carcinoma of the lung (SCCL). Int J Radiat Oncol Biol Phys 1986; 12: 771-777.

55) Inoue M, Miyoshi S, Yasumitsu T, Mori T, Iuchi K, Maeda H, Matsuda H. Surgical results for small cell lung cancer based on the new TNM staging system. Thoracic Surgery Study Group of Osaka University, Osaka, Japan. Ann Thorac Surg 2000; 70: 1615-1619.