

Follow-up of Patients Who Received Palliative Lung Radiotherapy: A Single Center Experience

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Abstract

Aim: This study conducted retrospectively aims to examine the relationship between survival time and some biochemical features in stage-4 patients who received palliative RT to their lungs.

Methods: Fifty-one patients who received palliative lung radiotherapy between July 2016 and May 2022 were included in the study. All patients; age, survival rate, gender and type of carcinoma [non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)]; some biochemical features were measured. For comparing groups, independent groups t-test and Mann-Whitney U test was used for normally and non-normally distributed features, respectively. Pearson correlation analysis was performed to determine the linear relationships between variables. Kaplan-Meier method was used to determine overall and groups' survival time.

Results: All patients had stage 4 LC, 41 (80.39%) of these were in the NSCLC group and 10 (19.61%) in the SCLC group. The overall median survival time was 16 weeks, while the survival time in the NSCLC and SCLC groups was 18 and 4 weeks, respectively. For the considered features, except for the ALT, no difference between the groups was found statistically significant. ALT values were approximately two times higher in the SCLC group.

Conclusions: The results of this study indicated that no significant relationship was found between survival time and considered biochemical features. However, it was observed that survival time of carcinoma groups was considerably different. Further research needs to examine more closely the relationships between survival time and some biochemical features in stage-4 patients who received palliative RT.

Keywords: Lung cancer; prognosis; radiotherapy; survival

1. Introduction

Lung cancer (LC) is the most commonly diagnosed malignancy and is the leading cause of cancer deaths worldwide. Non-small cell LC (NSCLC) accounts for the majority of LCs.¹ According to 2017 data in our country, the incidence of trachea, bronchi and LC in men is 596.7/100,000. Of the patients diagnosed with LC, 79.6% of them were NSCLC, while 16.5% of them were small cell LC (SCLC). 3.9% of LC patients consist of other rare pathologies. In our country, more than half of LC patients can only be diagnosed in the advanced stages of the disease, and distant metastases are observed in 56.5% of the patients at the time of diagnosis.² According to the National Cancer Institute, Surveillance, Epidemiology, and End Results, NSCLCs account for about 80% of newly diagnosed LC. Metastasis is seen in almost half of these patients at the time of diagnosis. Treatment of LC cases with metastases is very difficult; only 5% of these patients have a 2-year survival, and the average survival time is approxi-

mately 4–6 months.^{3,4}, depending on the patient population and treatment options. Treatment of stage-4 (S-4) disease is not curative but palliative. Despite chemotherapy (CT) and radiotherapy (RT), patients do not have a long survival. Palliative RT is performed for respiratory distress due to respiratory tract compression, hemoptysis, bone pain caused by bone metastases, neurological symptoms caused by brain metastasis or spinal cord compression.⁴

Treatment for NSCLC varies according to the patient's performance and stage.^{4,5} In the early stages (S-1, S-2) of the disease, lobectomy or pneumonectomy with standard mediastinal lymph node dissection and CT are performed within the indication. However, stereotactic body RT is performed for early-stage tumors where surgery is not medically possible. CT-RT is the standard treatment for locally advanced NSCLC that cannot be surgically performed. Otherwise, if patients with metastatic S-4 do not require RT for immediate

symptomatic palliation, CT is the standard treatment. In symptomatic conditions such as superior obstruction of the vena cava, hemoptysis, or cord compression, systemic treatment is performed after emergency RT. In addition, palliative RT is also applied to thorax, bone and brain metastases.^{5,6}

SCLC patients are treated according to whether the disease is limited-S and extensive-S disease at the time of diagnosis. While there is a survival of approximately 23 months in limited-S disease, a survival of approximately 8–9 months may occur in generalized S disease. In addition to the stage of the disease at the time of diagnosis, the survival of SCLC patients is also affected by the female sex factor, good performance status and normal lactate dehydrogenase (LDH) levels.^{5,6}

The aim of this study was to evaluate the relationship between survival time and some biochemical features in stage-4 patients who received palliative RT to their lungs.

2. Materials and Methods

This study was conducted retrospectively. Between July 2016 and May 2022, 51 patients with S-4-LC who were admitted to our hospital and received palliative RT for LC were included in the study. Before starting the study (Decision: 30.5.2022-6.10.2022/106-1953), ethics committee approval was obtained. The study was conducted by scanning all data in patient files in detail. Patients with metastatic LC and large tumor volumes who could not undergo curative RT, and patients with upper vena cava obstruction and hemoptysis were included in the study.

When looking at the performance status of the patients, 24 of 51 patients had an ECOG score 1, 20 had an ECOG score 2, and 7 had ECOG score 3. Twenty-two patients were receiving treatment for chronic obstructive pulmonary disease. Additionally, 17 patients had hypertension, 9 had type 2 diabetes mellitus, and 4 had coronary artery disease. The study's preliminary data on 45 patients were presented as an oral presentation at the III International Congress of Applied Statistics.

Patients' age, survival time after RT (defined as weeks), gender, and type of carcinoma (NSCLC and SCLC); Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Sodium (Na), Potassium (K), Hematocrit value (HCT), Hemoglobin (HGB), Lymphocyte (LYM), Neutrophil (NEU), Urea, White blood cell (WBC) and Lactate dehydrogenase (LDH) values were measured.

2.1. Chemotherapy

In patients with stage-4 NSCLC cancer; EGFR, ALK, ROS-1 and PD-L1 were examined. Patients with EGFR mutation or deletion were given afatinib as first-line treatment⁷. Brigatinib was used in patients with ALK rearrangement⁸. Crizotinib was used in patients with ROS-1 rearrangement⁹. Patients with PD-L1 ≥50% were treated with pembrolizumab. In patients with LC adenocarcinoma with PD-L1 ≥1%–49%, carboplatin or cisplatin + pemetrexed + pembrolizumab were used^{10,11}. Patients with LC squamous cells with PD-L1 ≥1%–49% were given carboplatin + paclitaxel + pembrolizumab^{12,13}. In patients with progression, if the patient did not receive immunotherapy in the first line, they received nivolumab in the second-line treatment^{8,14}. In the treatment of common S-SCLC cancer, some of the patients received carboplatin, etoposide and atezolizumab. Atezolizumab was used as maintenance therapy¹⁵. Some of the patients received irinotecan as second-line therapy after cisplatin and etoposide^{16,17}.

2.2. Radiotherapy

External palliative RT was performed with 30 Gy (10 fractions) of the intensity-modulated radiotherapy treatment method for LC masses in 51 patients with the diagnosis of S-4 LC and symptoms of

LC mass.

2.3. Statistical analysis

Descriptive statistics for the continuous variables were presented as mean, standard deviation, minimum and maximum values, while for categorical variables they were given as count and percentages. Kolmogorov–Smirnov normality test was performed, and threshold values for significance were evaluated before group comparisons for continuous variables. Following the normality test, independent groups t-test was used for normally distributed variables and Mann–Whitney U test was used for non-normally distributed variables to compare groups. Pearson correlation analysis was performed to determine the linear relationships between variables. Kaplan–Meier method was used to determine overall and groups' survival time. The statistical significance level was considered as 5%, and SPSS (ver: 21) statistical package program was used for all statistical computations

3. Results

All of the patients had S-4 LC cancer, 13 (25.49%) patients were female and 38 (74.50%) were male. A total of 41 (80.39%) patients had NSCLC [15 (36.58%) adenocarcinoma pathology, 26 (63.41%) squamous carcinoma pathology] and 10 (19.60%) patients had SCLC pathology. The overall distribution showed that the majority of cases were NSCLC, whereas a smaller proportion of patients presented with SCLC, which is consistent with the expected epidemiology of advanced lung cancer.

Table 1

Comparison of clinical and biochemical features by gender

Variable	Female (n=13) Mean ± SD	Male (n=38) Mean ± SD	p
Age (years)	65.25 ± 7.64	63.84 ± 10.04	0.658
HGB (g/dL)	11.50 ± 0.85	11.32 ± 1.64	0.728
LYM	1.40 ± 0.72	0.97 ± 0.68	0.077
NEU	7.55 ± 5.66	7.11 ± 5.43	0.811
WBC	10.68 ± 5.05	9.22 ± 5.11	0.410
HCT (%)	34.55 ± 5.26	35.01 ± 4.98	0.783
Urea (mg/dL)	40.77 ± 36.47	39.32 ± 20.66	0.865
K (mg/dL)	3.98 ± 0.64	4.17 ± 0.55	0.311
Na (mg/dL)	134.38 ± 2.00	136.42 ± 4.66	0.148
ALT (U/L)	35.30 ± 42.54	28.05 ± 27.94	0.501
LDH (U/L)	290.36 ± 139.04	249.21 ± 96.06	0.279
AST (IU/L)	39.99 ± 30.10	34.38 ± 34.35	0.629
Survival (weeks)	9.00 ± 6.09	16.24 ± 8.66	0.010

Age [Years], Hemoglobin [HGB, g/dL], Lymphocyte [LYM], Neutrophil [NEU], White Blood Cell [WBC], Hematocrit [HCT, %], Urea [mg dL], Potassium [K, mg /dL], Sodium [Na, mg /dL], ALT [U/L], LDH [U/L], AST [IU/L], Overall Survival [week]

†: Man-Whitney U test, º: Independent t test

For gender, Table 1 summarizes descriptive statistics and comparison results of the considered features in the study. As can be seen, the differences between male and female patients were not statistically significant for most variables. However, the difference in survival time was statistically significant. The mean survival time of male patients was 16 weeks, whereas it was 9 weeks in female patients ($p=0.010$). Accordingly, male patients survived significantly longer than female patients.

Table 2

Comparison of clinical and biochemical features by carcinoma type

Variable	NSCLC (n=41) Mean \pm SD	SCLC (n=10) Mean \pm SD	p
Age (years)	63.51 \pm 9.57	67.22 \pm 8.86	0.292
HGB (g/dL)	11.35 \pm 1.51	11.42 \pm 1.49	0.892
LYM	1.09 \pm 0.72	1.00 \pm 0.65	0.740
NEU	6.75 \pm 5.32	9.26 \pm 5.79	0.216
WBC	9.29 \pm 5.23	10.68 \pm 4.47	0.468
HCT (%)	34.63 \pm 5.10	36.09 \pm 4.60	0.435
Urea (mg/dL)	42.46 \pm 26.48	27.64 \pm 12.88	0.111
K (mg/dL)	4.17 \pm 0.57	3.91 \pm 0.57	0.215
Na (mg/dL)	136.01 \pm 4.50	135.48 \pm 2.97	0.738
ALT (U/L)	23.33 \pm 21.68	58.14 \pm 51.21	0.002
LDH (U/L)	268.66 \pm 117.33	223.89 \pm 50.20	0.273
AST (IU/L)	31.41 \pm 31.75	53.78 \pm 34.80	0.068
Survival (weeks)	16.88 \pm 7.69	3.67 \pm 0.71	0.001

Age [Years], Hemoglobin [HGB, g/dL], Lymphocyte [LYM], Neutrophil [NEU], White Blood Cell [WBC], Hematokrit [HCT, %], Urea [mg dL], Potassium [K, mg /dL], Sodium [Na, mg /dL], ALT [U/L], LDH [U/L], AST [IU/L], Overall Survival [week], †: Man-Whitney U test, ‡: Independent t test

For the considered features in the study, descriptive statistics and comparison results to carcinoma type are presented in Table 2. It can be seen from the data in Table 2 that the difference between the means according to the type of carcinoma in terms of survival time and other characteristics (variables) other than ALT was not statistically significant. The mean survival time was 16.88 weeks in patients with NSCLC and 3.67 weeks in patients with SCLC. From the data in Table 2, it is apparent that the survival time in NSCLC group patients is approximately 4 times longer than the survival time in SCLC group patients ($p=0.001$). This difference was found to be statistically significant.

The mean values for ALT were 23.33 in the NSCLC group and 58.14 in the SCLC group. The difference between the NSCLC and SCLC groups was statistically significant ($p=0.002$), and ALT values were markedly higher in patients with SCLC than in the NSCLC group.

The correlation coefficients between the features are given in Table 3. As can be seen from Table 3, the highest correlation was observed between HGB and HCT with 93.3%, followed by the correlation between NEU and WBC with 93.1%. A statistically significant ($p<0.05$) positive correlation was observed between age with LYM and HCT. A negative correlation was found between age with NEU, WBC and Urea ($p<0.05$). Although not statistically significant, the highest negative correlation detected with survival time was between age and survival (26.7%).

Table 3

Significant correlations between clinical and biochemical features

Variables correlated	Correlation (r)	Significance
HGB – HCT	0.933	$p<0.01$
NEU – WBC	0.931	$p<0.01$
Age – LYM	0.432	$p<0.01$
Age – HCT	0.289	$p<0.05$
Age – NEU	-0.429	$p<0.01$
Age – WBC	-0.367	$p<0.05$
Age – Urea	-0.360	$p<0.05$
Age – Survival	-0.267	n.s.

*: $p<0.05$; **: $p<0.01$

Summary results of survival analysis by groups are illustrated in Table 4. In all patient group included in the study, the mean survival time was 16.3 weeks, while the median survival time was 16 weeks (95% confidence interval for mean time to survival; it ranged from 13.429 weeks to 19.171 weeks, while the median survival interval of 95% was between 10.06 weeks and 21.94 weeks). Table 4 shows that when examined according to carcinoma groups; in the NSCLC group, the mean survival time was 19.073 weeks and the median survival time was 18 weeks (the 95% confidence interval for mean and median survival times was found to be between 16.202 and 21.944 and 11.08 and 22.02, respectively). In the SCLC group, the mean and median survival times were found to be 3.667 and 4 weeks, respectively (95% confidence intervals were in the range of 3.205–4.129 and 3.538–4.462). The difference between the carcinoma groups in terms of survival times was statistically significant ($p<0.05$), and it was observed that the survival time was approximately four times higher in the NSCLC group compared to the SCLC group.

Table 4

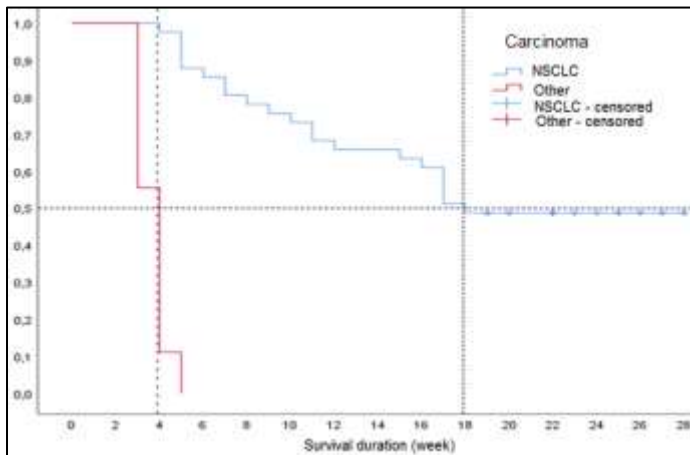
Survival analysis by carcinoma type

Group	Mean Survival (weeks) \pm SE	Median Survival (weeks) \pm SE	95% CI (mean)	95% CI (median)	p-value
NSCLC	19.07 \pm 1.46	18.0 \pm 3.37	16.20–21.94	11.08–22.02	0.001
SCLC	3.67 \pm 0.24	4.0 \pm 0.24	3.20–4.12	3.54–4.46	
All	16.30 \pm 1.46	16.0 \pm 3.03	13.43–19.17	10.06–21.94	

When Figure 1, in which the survival graph is given according to carcinoma groups, is examined; it can be said that half (50%) of the patients in the NSCLC group can only survive until the 18th week, while half of the patients in the SCLC group can only live until the 4th week. In other words, patients with metastatic LC who received palliative RT and had SCLC histology died markedly earlier, with 50% of them dying before the fourth week.

Figure 1

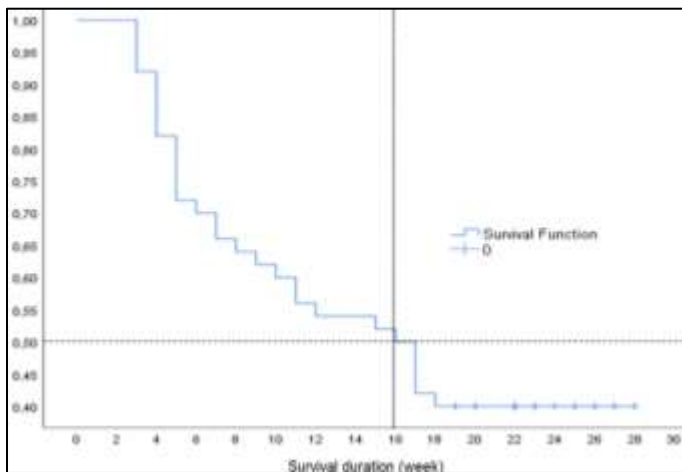
Survival graphic by carcinoma type (NSCLC and SCLC)



From the data in Figure 2, where the survival graph is given for all patients, it is apparent that 50% of the patients die after the sixteenth week or only half of the patients survive until the sixteenth week. In other words, half of the S-4 LC patients who received palliative RT for LC died after 16 weeks, indicating the generally poor prognosis of this patient population.

Figure 2

Survival graphic for all patient



4. Discussion

If cough, hemoptysis, chest wall pain, superior vena cava obstruction, hoarseness, dyspnea due to airway obstruction occur in LC patients, palliative RT is given for the mass^{1,5,6}. Systemic therapy is the first treatment to be given as a standard and supportive treatment except for emergency LC-RT in case of local symptoms that require palliative RT for the LC mass in patients with S-4 LC. Since the prognosis of S-4 LC patients is quite rapid and poor, treatment should be started immediately after the diagnosis of LC.

NSCLC and SCLC are important for the patient's age, hemogram, blood biochemistry, female and male. Blood biochemical values of the patients are given in Tables 1 and 2. What stands out in Table 1 is the survival time of male patients was longer than the sur-

vival time of female patients ($p=0.010$)¹⁸. In previous studies, the survival time of patients receiving palliative LC RT is quite short^{19,20,21}. In our study, the survival time was found to be 3.67 weeks in patients with metastatic SCLC (Table 2). The mean survival time was 16.88 weeks in the S-4 NSCLC group patients who underwent palliative RT for LC (Table 2). In a study conducted in the USA, it was shown that the treatment of patients was affected due to the presence of patients based on different populations, socio-demographic factors (such as age), clinical factors, and financial structures²¹. In our study, the treatment of the patients was not affected. This situation; Although there is a limited number of patients, it can be associated with the close age group and the fact that the patients were taken from the homogeneous population. Nevertheless, the mean survival of 16.88 weeks observed in our NSCLC cohort appears shorter than the 4–6 months reported in the literature²², and this may be related to the predominance of advanced stage disease, poor performance scores, and multiple comorbidities in our patient population²³.

In our study, although it was not statistically significant, the highest negative correlation with survival time was between age and survival (26.7%) (Table 3). Accordingly, it can be said that patients with advanced LC and S-4 disease will not have long survival despite receiving palliative RT for LC. In a predetermined analysis for histological type squamous and non-squamous related survival, survival was reported in patients with a non-squamous histological type (median OS, 11.8 versus 10.4 months). Despite treatment for metastatic NSCLC, the mean survival is 4-6 months and only 5% of patients have a 2-year survival²¹.

CT is the mainstay of SCLC treatment. SCLC is a highly aggressive and diffuse metastatic malignancy. Most of the disease occurs in heavy smokers or those who have used it before. Worldwide, the 5-year survival rate for SCLC is only about 7%. It is estimated that it causes 250 000 deaths annually. SCLC is characterized by rapid growth, high vascularity, genomic instability, and early metastasis^{1,5,24}. In our study, the mean and median survival times were found to be 3.667 and 4 weeks, respectively, in SCLC patients who underwent RT for palliative LC mass (Table 4).

It can be said that half (50%) of the patients in the NSCLC group only survive until the 18th week, while half of the patients in the SCLC group only survive until the 4th week (Table 4, Figure 1). The mean survival time was 16.3 weeks, while the median survival time was 16 weeks. The difference between carcinoma groups in terms of survival times was found to be statistically significant ($p<0.001$), and survival time was approximately 4 times higher in the NSCLC group than in the SCLC group (Table 4). In our study, 50% of the patients died after the 16th week, in other words, only half of the patients survived until the 16th week (Figure 2).

Treatment of metastatic E-4 NSCLC is palliative rather than curative. In the presence of symptoms that require palliation, they receive palliative RT when they suffer from their illness^{5,23}. Targeted therapies in S-4 NSCLC cancer significantly prolong survival, but the proportion is low in current patients⁶. In our study, although ALT levels were significantly higher in the SCLC group, this biochemical difference did not translate into a survival advantage, and this finding highlights the need for further biological explanation and investigation. Elevated ALT in SCLC may be related to more frequent liver involvement, paraneoplastic hepatic enzyme induction, or aggressive tumor metabolism²⁴, which warrants further mechanistic studies. Thanks to the advent of newly developed immunotherapy and targeted agents, the number of combination options for NSCLC treatment has increased. This suggests an increased response to combination of CT and immunotherapy in patients with NSCLC. Patients who received CT had a longer survival time than those who received supportive care. It has been found to be a prognostic factor,

especially in young NSCLC patients, regardless of stage and treatment modalities²⁵. With new chemotherapy and immunotherapy combinations, 5-year survival rates have reached 20%²⁵. The 5-year survival rate for S-4 NSCLC is about 8%. Patients with high PDL-1 levels appear to have a better response to immunotherapy and longer survival^{10,11}. In disseminated S-SCLC cancer, the combination of CT and immunotherapy has a higher survival rate than patients who receive CT alone. It is seen that new studies and biomarkers are needed to identify patients who will benefit from immunotherapy^{15,16,17}.

In S-4 NSCLC and disseminated S-SCLC cancer, RT given to the primary mass provides benefits for pain palliation, bleeding and pressure symptoms. It has an effect on improving the quality of life of patients. It has minimal effect on survival.

Our single-center retrospective study with a small number of patients encountered some limitations due to the small sample size and poor patient performance.

5. Conclusion

Both survival and quality of life of the patient are increased by better understanding of tumor biology and early RT decision in metastatic disease and initiation of systemic treatment, rather than differentiating LC treatment, SCLC or NSCLC. In the study, it was tried to determine the relationship between survival and some biochemical characteristics in S-4 LC patients who received palliative RT. It was observed that the survival time of male patients was longer than the survival time of female patients. Survival time in NSCLC group patients was found approximately 4 times higher than SCLC group patients. The difference between carcinoma groups in terms of survival time was found statistically significant ($p < 0.05$). Palliative RT is an effective treatment for E-4 LC patients to relieve symptoms such as hemoptysis, bronchial obstruction, cough, chest pain, and shortness of breath. It is important to provide early palliation in these patients with short survival time.

In summary, the results of this study showed that no significant relationship was found between survival time and considered biochemical features in the study. However, ALT was significantly higher in SCLC patients, which indicates that some biochemical parameters may still carry prognostic value and should be investigated in larger studies. Whereas, it was observed that survival time of carcinoma groups was considerably different. However, further research needs to examine more closely the relationships between survival time and some biochemical features in stage-4 patients who received palliative RT.

Statement of ethics

Before starting the study, ethics committee was obtained from Adana City Training and Research Hospital Ethics Committee with the numbers 30.5.2022-6.10.2022/106-1953

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

Author contributions

All authors contributed equally to the article. All authors read and approved the final manuscript.

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