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ORIGINAL ARTICLE

Survival Outcomes in Limited-stage Small Cell Lung Cancer Treated with Chemoradiotherapy

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OBJECTIVE

The aim of this study is to examine the survival outcomes in limited-stage small-cell lung cancer (SCLC) treated with definitive chemoradiotherapy and to evaluate the prognostic factors that may affect survival.

METHODS

83 patients diagnosed with limited-stage SCLC were identified retrospectively. Demographic features, clinical information, hemoglobin level, lactate dehydrogenase, C-reactive protein, and albumin levels were recorded. Kaplan–Meier method was used to calculate overall survival (OS), progression-free survival (PFS), and local regional recurrence-free survival (LRRFS), and differences were assessed using the Log-rank test. The Cox proportional hazard regression model was performed to evaluate the potential prognostic variables.

RESULTS

Thoracic radiotherapy was given with 1st or 2nd chemotherapy in 68.7% of the patients. Prophylactic cranial irradiation (PCI) was applied to 45.9% of the patients. At a median follow-up of 14 (3–83) months, 5 of the patients were alive at the final follow-up. Disease recurrence was observed in 31 patients, distant metastases were detected in 51 patients. Median and 2-y OS, PFS and LRRFS were 16, 11, and 14 months and 31.8%, 20.5%, and 26.9%, respectively. Hypoalbuminemia was found to affect PFS and LRRFS in univariate analysis (p=0.033, p=0.044). In subgroup analysis, PCI was effective on OS (p=0.045). In multivariate regression analysis, no significant relationship was found between PCI and OS (p=0.055), hypoalbuminemia was statistically significant on PFS and LRRFS (p=0.022, p=0.032).

CONCLUSION

With the addition of PCI to the treatment, there was a tendency to improve in terms of OS. Low albumin level at the time of diagnosis was found to negatively affect PFS and LRRFS.

Keywords: Chemoradiotherapy; hypoalbuminemia; prognosis; prophylactic cranial irradiation; small-cell lung cancer; survival.

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INTRODUCTION

Lung cancer is still one of the leading cancer-related deaths worldwide.[1] Small-cell lung cancer (SCLC) constitutes approximately 15% of all lung cancer cases. The proportion of patients who can be diagnosed in the limited stage is very low, accounting for only one-third of cases.[1] Definitive chemoradiotherapy (CRT) and chemotherapy are the accepted standard treatment modalities in limited-stage SCLC.[2,3] In responding cases, prophylactic cranial irradiation (PCI) is routinely added to standard therapy, especially since it contributes to survival.[2,3]

Despite the treatments applied in SCLC, which has the potential for early metastatic spread and has an aggressive course, the survival rates cannot be as high as desired.[4] Therefore, there is a need for prognostic markers that can identify high-risk patients and predict survival. Prognostic markers related to survival have been examined in many studies to date, age, gender, performance status, tumor stage, the timing of radiotherapy (RT), PCI, lactate dehydrogenase (LDH), and C-reactive protein (CRP) are some of these markers.[5-16] The most important prognostic factor among these is the stage. Although SCLC has traditionally been staged according to the Veterans Affairs classification, the tumor-node-metastasis (TNM) classification has also been found to be prognostic for survival and direct correlation between both T and N stage and survival has been demonstrated.[5] In addition, it is known that the prognosis worsens as the tumor volume increases.[6] Previous data have explained that good performance status, younger age, and female gender are associated with improved prognosis.[7-9] Other prognostic factors are timing of RT and administration of PCI.[10-14] The early timing of RT with the first or second cycle of chemotherapy is superior to delayed RT, with significant results on survival.[10-12] In two consecutive meta-analyses published before the 2000s, PCI was shown to reduce the frequency of brain metastases and also improve survival.[13,14] In addition to patient- and treatment-related factors, several routine laboratory tests have been associated with survival, including LDH, CRP, albumin, sodium, creatinine, and bilirubin, and pre-treatment evaluation with these laboratory tests is useful in predicting survival.[15,16]

In this retrospective study, we aimed to examine the survival outcomes in limited-stage SCLC treated with definitive CRT and to evaluate the prognostic factors that may affect survival.

MATERIALS AND METHODS

Study Design and Patient Characteristics

Patients with limited-stage SCLC who underwent definitive CRT at the Health Sciences University Samsun Training and Research Hospital Radiation Oncology Clinic between January 2012 and December 2020 were included in the study. Patients who are older than 18 years of age, have a pathological diagnosis, have undergone definitive CRT, and have an Eastern Cooperative Oncology Group performance status of 0–1 are inclusion criteria. Patients with extensive-stage SCLC, patients who did not receive concomitant chemotherapy, and patients who could not complete RT were not included in the study.

98 patients diagnosed with limited-stage SCLC were identified, and 83 patients were included in the study after excluding 15 patients who did not receive concomitant chemotherapy and received consolidation RT alone. The demographic and clinical characteristics of patients are displayed in Table 1. The majority of the patients were male (84.3%) and the median age was 61 (36-84). 31.9% of the patients were in the T4 stage and 74.3% were in the N2 stage. According to the American Joint Committee on Cancer (AJCC), the majority of patients were stage 3 (81.9%). Median 60 Gy (50-66 Gy) RT was applied. Thoracic RT was given with 1st or 2nd chemotherapy in 68.7% of the patients, and it was applied sequentially in 31.3% of the patients. PCI was applied to 45.9% of the patients. PCI was not performed in 38.5% of the patients due to progression and/or brain metastasis. PCI could not be performed in 15.6% of the patients due to patient preference or not being referred by the physician.

Approval was obtained from the ethics committee of our hospital for our study, data were collected in accordance with the Declaration of Helsinki, and informed consent was not obtained because it was a retrospective study.

Data Collection

Demographic features, clinical information, and laboratory data of the patients were accessed through the patient archive files and electronic medical records system. Hemoglobin (Hb) level, LDH, CRP, and albumin levels were recorded. Hb level <12 was defined as anemia, LDH >225 U/L as elevated LDH, CRP >5 mg/L as elevated CRP, and albumin <35 g/L as hypoalbuminemia, and the values were categorized.

Staging and Treatment

Thorax computed tomography (CT) and CT of the whole abdomen were performed in all patients for di-

Table 1 Patient characteristics

Variable	n	%
Gender		
Female	13	
Male	70	
Age		
<60	36	43.4
≥60	47	56.6
T stage		
T1–2	32	38.6
T3–4	51	61.4
N stage		
N0-1	14	16.8
N2-3	69	83.2
Timing of RT		
1./2. CT	57	68.7
≥3. CT	26	31.3
PCI		
Yes	34	45.9
No	49	54.1

RT: Radiotherapy; CT: Computed tomography; PCI: Prophylactic cranial irradiation

agnosis and staging. Positron emission tomography/CT (PET CT) was performed in some of the patients for distant metastasis screening. Brain magnetic resonance imaging (MRI) was performed to scan for brain metastasis. The patients were classically staged according to the Veterans Affairs Lung Study Group, and TNM stages were also noted according to the 8th edition of the AJCC.

Definitive CRT was applied concurrently with the first or second chemotherapy in the majority of the patients, and sequential CRT was applied in some of the patients because the tolerance doses of the critical organs due to the high treatment volume could not be achieved. Thoracic RT was administered with a three-dimensional conformal technique, with a median of 60 Gy (50-66) at 1.8-2 Gy/fraction. Gross tumor volume was drawn by drawing the primary mass and involved lymph nodes. In patients who received chemotherapy, the target volumes were determined according to the post-chemotherapy volumes. The clinical target volume was formed with the volume created by expanding this defined volume by 0.5-0.8 cm. To prevent possible set-up errors and changes due to respiratory movements, the planning target volume was created by giving this volume a margin of 1-2 cm, depending on the location of the primary mass. Position accuracy was ensured by the kV imaging taken during the treatment. Concurrently with RT, cisplatin 75 mg/m^2 (1 days), etoposide 100 mg/m^2 (1-3 days) 1 or 2 cycles of chemotherapy were administered at 21-day intervals. PCI was administered with a three-dimensional conformal technique, with a total dose of 25 Gy in 10 fractions.

Follow-up

The first evaluation with thorax CT was performed 1 month after the completion of CRT. Patients who completed chemotherapy courses and achieved complete or partial response were re-evaluated with brain MRI, and PCI was applied to patients without metastases. Physical examination, blood samples including blood count and biochemical tests, chest X-ray or thorax CT were followed up every 3 months for the first 2 years and then every four to 6 months. In case of clinical necessity, PET CT and brain MRI were performed. Response assessment was performed according to the Response Evaluation Criteria for Solids Tumors ver.1.1. Patients were followed up regularly from the date of diagnosis to March 2022, or the date of death. The primary endpoints of the study were overall survival (OS), progression-free survival (PFS), and local regional recurrence-free survival (LRRFS). Secondary endpoints were to identify all prognostic factors such as stage, the timing of RT, and PCI. In addition, to avoid potential bias, a subgroup of patients who underwent PCI and did not undergo PCI due to patient demand or non-referral by a physician was defined.

OS was defined as the interval from the date of diagnosis to the date of death or last follow-up. PFS was calculated as the interval from the date of diagnosis to the date of disease progression or death or last follow-up. LRRFS was calculated as the interval from the date of diagnosis to the local recurrence, death, or last follow-up.

Statistical Analysis

SPSS version 25.0 (IBM Corp., Armonk, NY, USA) software was used for statistical analysis. Categorical variables were expressed as numbers and percentages, continuous variables were displayed as medians. Kaplan-Meier method was used to calculate OS, PFS, and LRRFS, and differences were assessed using the Log-rank test. The Cox proportional hazard regression model was performed to evaluate the potential prognostic variables. $P<0.05$ was indicated statistical significance.

RESULTS

At a median follow-up of 14 (3-83) months, 5 of the patients were alive at the final follow-up. While primary disease recurrence was observed in 31 patients, distant

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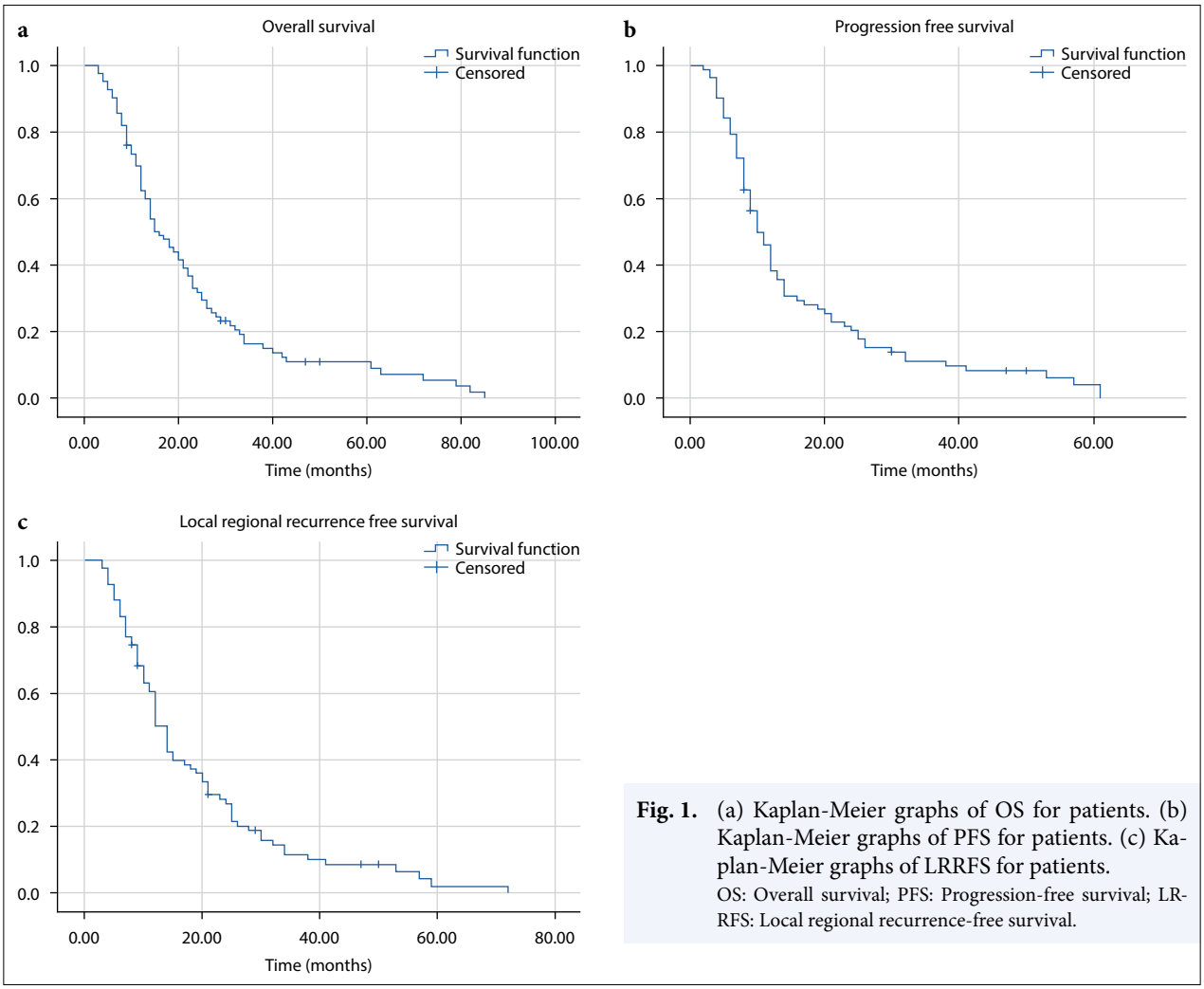

Fig. 1. (a) Kaplan-Meier graphs of OS for patients. (b) Kaplan-Meier graphs of PFS for patients. (c) Kaplan-Meier graphs of LRRFS for patients.
OS: Overall survival; PFS: Progression-free survival; LRRFS: Local regional recurrence-free survival.

metastases were detected in 51 patients. Median OS was 16 months (95% CI, 11.9-23.3), 1-y, 2-y, and 4-y OS rates were 62.4%, 31.8%, and 10.9% (Fig. 1a). In univariate analysis, gender (p=0.546), age (p=0.936), tumor stage (p=0.678), tumor size (p=0.856), nodal stage (p=0.740), RT dose (p=0.249), timing of RT (p=0.331), hypoalbuminemia (p=0.081), anemia (p=0.723), LDH (p=0.914), and CRP (p=0.517) were not found to be effective on survival. In subgroup analysis, median OS was 26 months (95% CI, 18.2-33.7). PCI was statistically significant on OS, with 2-y OS rates of 62.5% and 27.5% (p=0.045; 31 months vs. 19 months) (Table 2 and Fig. 2a). There was a trend on survival with PCI, but not statistically significant in multivariate regression analysis (p=0.055; HR 2.11 95% CI 0.98-4.53) (Table 3).

Median PFS was 11 months (95% CI, 9.1-12.8), and 1-y, 2-y, and 4-y PFS rates were 38.5%, 20.5%, and 8.5% (Fig. 1b). In univariate analysis, gender (p=0.719), age (p=0.586), tumor stage (p=0.538), tumor size (p=0.225), nodal stage (p=0.966), RT dose (p=0.203), timing of RT (p=0.251), anemia (p=0.714), LDH (p=0.940), and CRP (p=0.886) were not found to be effective on survival. Hypoalbuminemia was found to be statistically significant on PFS (p=0.033) (Table 2 and Fig. 3a). In multivariate regression analysis, hypoalbuminemia was independently prognostic on PFS (p=0.022; HR 2.24 95% CI 1.12-4.48) (Table 3). In subgroup analysis, median PFS was 19 months (95% CI, 13.3-24.6). The median PFS was 21 versus 14 months in patients with and without PCI, but this difference was not statistically significant in the univariate analysis (p=0.271) (Fig. 2b).

Median LRRFS was 14 months (95% CI, 12.1-15.8), and 1-y, 2-y, and 4-y LRRFS rates were 50.2%, 26.9%, and 8.7% (Fig. 1c). In univariate analysis, gender (p=0.397), age (p=0.168), tumor stage (p=0.589), tumor size (p=0.736), nodal stage (p=0.337), RT dose (p=0.726), timing of RT (p=0.139), anemia (p=0.885),

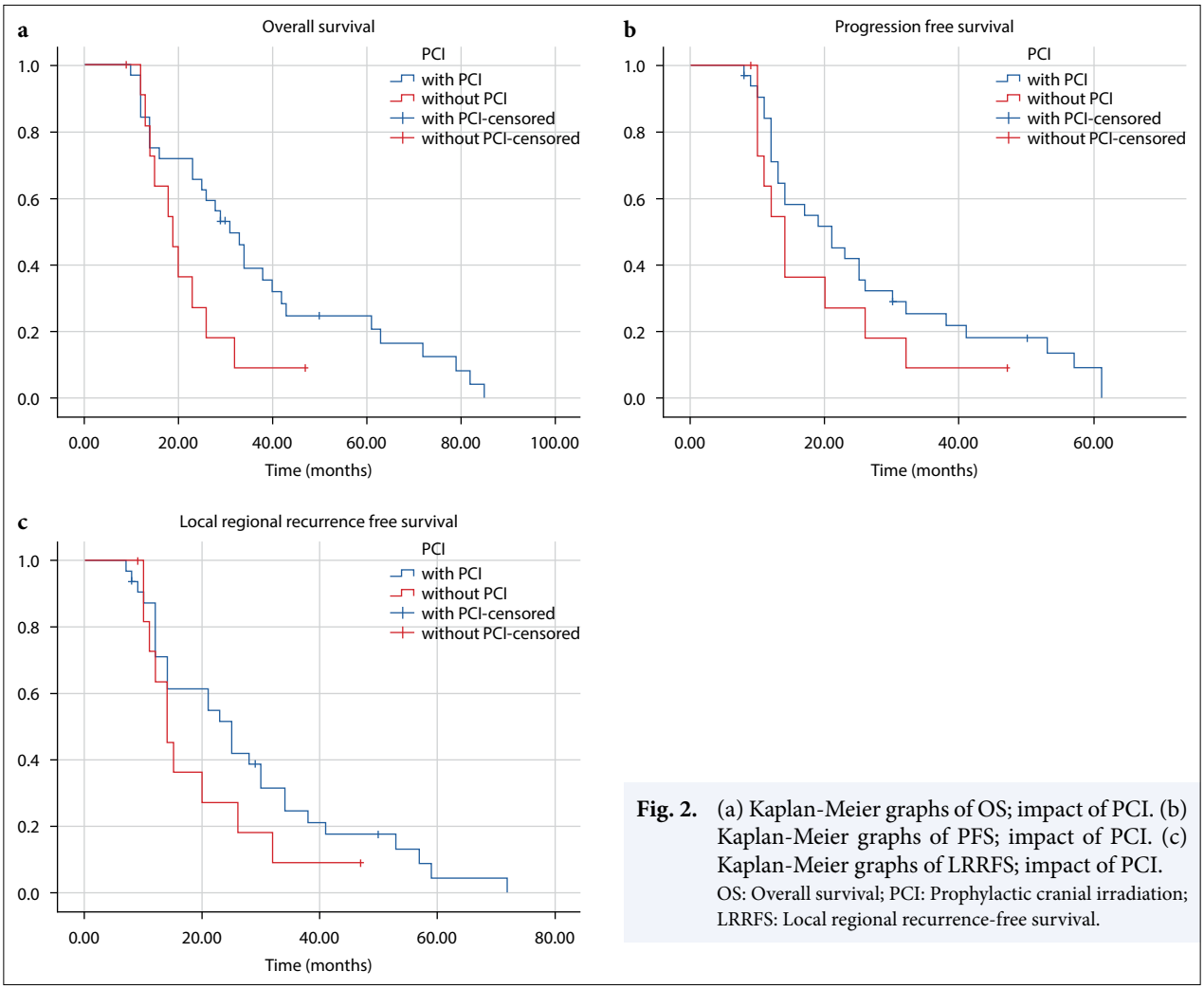

Fig. 2. (a) Kaplan-Meier graphs of OS; impact of PCI. (b) Kaplan-Meier graphs of PFS; impact of PCI. (c) Kaplan-Meier graphs of LRRFS; impact of PCI.
OS: Overall survival; PCI: Prophylactic cranial irradiation; LRRFS: Local regional recurrence-free survival.

LDH (p=0.494), and CRP (p=0.579) were not found to be effective on survival. Hypoalbuminemia (p=0.044) was found to be statistically significant on LRRFS (p=0.017; 14 months vs. 9 months) (Table 2 and Fig. 3b). In multivariate regression analysis, hypoalbuminemia was shown to be independently prognostic on LRRFS (p=0.032; 2.08 (1.06-4.08) (Table 3). In subgroup analysis, the median LRRFS was 21 months (95% CI, 12.3-29.7). There was no difference between the groups in terms of LRRFS with the application of PCI (p=0.196) (Fig. 2b).

DISCUSSION

In our single-center retrospective study, survival outcomes in limited-stage SCLC treated with definitive CRT were evaluated and its relationship with factors affecting survival was examined. PCI was found to be prognostic on OS in univariate analysis, but failed to show an association with OS in multivariate analysis. Low albumin levels at the time of diagnosis were also found to negatively affect PFS and LRRFS.

The strengths of this study are as follows. Extensive stage patients and patients who were not given concomitant chemotherapy were not included in the study concept. In addition, patients with a performance status of at most 1 were included in the study because low survival rates are known to be associated with poor performance. So a more homogeneous patient group could be formed.

The fact of PCI in SCLC is based on the following findings from historical studies.[13,14] The risk of brain metastases is quite high in SCLC patients. Chemotherapy agents used in the standard treatment of SCLC cannot penetrate the blood-brain barrier. Although SCLC patients respond well to chemotherapy, a high rate of brain metastases is encountered due to

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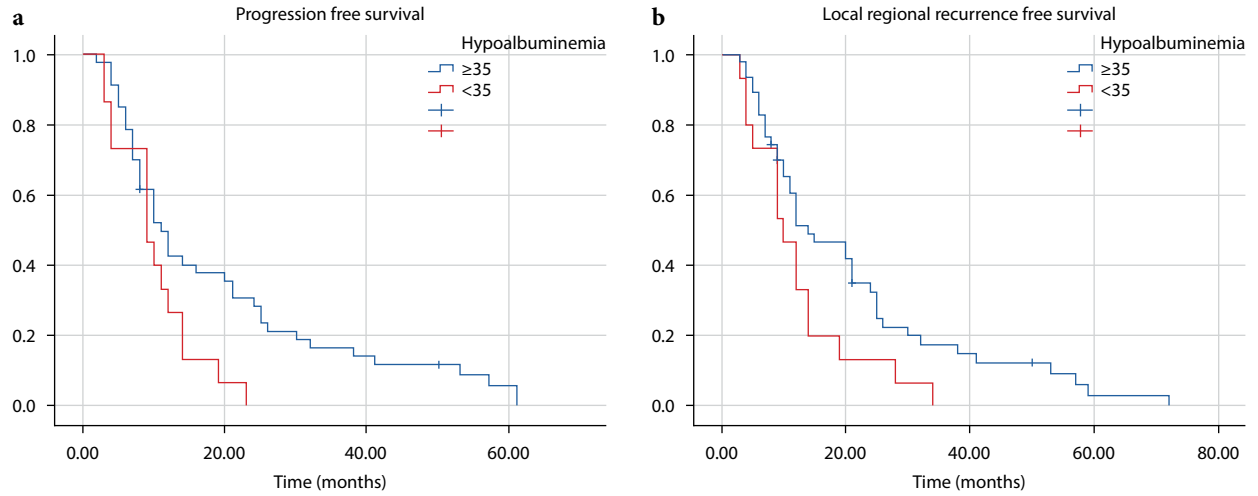

Fig. 3. (a) Kaplan-Meier graphs of PFS; impact of hypoalbuminemia. (b) Kaplan-Meier graphs of LRRFS; impact of hypoalbuminemia.
PFS: Progression-free survival; LRRFS: Local regional recurrence-free survival.

the limited effectiveness of chemotherapy agents to the central nervous system. A significant contribution of OS has been demonstrated with PCI for this purpose. In a meta-analysis published in 1999, it was reported that the incidence of 3-y brain metastasis decreased with PCI (58.6% vs. 33.3%), 3-y OS increased significantly from 15.3% to 20.7%.[13] Subsequently, a second meta-analysis was published in 2001 showing the contribution of PCI to survival by reducing the incidence of brain metastases.[14] In this context, PCI has been an accepted treatment approach for many years in the treatment of limited-stage SCLC, as it both increases survival and reduces the development of brain metastasis. In our study, it was determined that PCI contributed positively to survival in univariate analysis, but it did not show a relationship with OS in multivariate analysis.

However, an important consideration is response assessment prior to PCI implementation. PCI is recommended in patients with a complete or partial response to the primary disease. In the patients included in our study, PCI was not performed due to the detection of progression and/or brain metastasis in 38.5% of the patients during restaging. On the other hand, PCI could not be performed in 15.6% of the patients due to patient preference or not being referred by the physician. While PCI contributes significantly to survival, the decrease in neurocognitive functions is an undeniable side effect and therefore may not be accepted by patients. It has been shown that the radiation dose given to the hippocampus is associated with neurocognitive toxicity, and in this context, hippocampus-sparing treatment approaches were primarily investigated in patients receiving whole-brain RT for brain metastases.[17] In a recently published phase 3 study, 150 SCLC patients were randomized to hippocampal avoidance-PCI or standard PCI and showed significantly better neurocognitive function in the hippocampal avoidance-PCI arm (5.8% vs. 23.5%, p=0.003).[18] It was also stated that there was no difference between the two arms in terms of local brain failure and OS, which were the secondary endpoints of the study. There are also drugs being investigated to preserve neurocognitive functions. 518 patients with brain metastases were randomized to hippocampal avoidance plus memantine or whole-brain RT plus memantine. This phase 3 study demonstrated improved neurocognitive functions with hippocampal avoidance plus memantine, with no difference between groups in terms of PFS and OS. Since successful results have been obtained with the use of memantine to preserve neurocognitive functions, it is now recommended for whole-brain RT.[19,20] The decrease in neurocognitive functions due to PCI is beyond the scope of our study, but it should be applied to all patients knowing that this concern can be relieved with alternative methods instead of avoiding PCI.

Another important prognostic factor in limited-stage SCLC is the early timing of thoracic RT. A meta-analysis of 2140 patients with limited-stage SCLC including 13 studies showed a 14% reduction in mortality with combined treatment with thoracic RT compared

Table 2 Univariate analysis for overall survival, progression-free survival, and local regional recurrence free survival

	OS	PFS	LRRFS
Variable	**p**	**p**	**p**
Age			
<60 versus ≥60	0.936	0.586	0.168
Gender			
Male versus Female	0.546	0.719	0.397
T stage			
T1-2 versus T3-4	0.678	0.538	0.589
N Stage			
N0-1 versus N2-3	0.740	0.966	0.337
Tumor size (cm)			
<5cm versus ≥5cm	0.856	0.225	0.736
Timing of RT			
1./2. CT versus ≥3. CT	0.331	0.251	0.139
RT dose (Gy)			
<60 versus 60 versus ≥60	0.249	0.203	0.726
Albumin			
≥35 versus <35	0.081	**0.033**	**0.044**
Hb			
≥12 versus <12	0.723	0.714	0.885
LDH			
<225 versus ≥225	0.914	0.940	0.494
CRP			
<5 versus ≥5	0.517	0.886	0.579
PCI			
+versus-	**0.045**	0.271	0.196

OS: Overall survival; PFS: Progression-free survival; LRRFS: Local regional recurrence-free survival; RT: Radiotherapy; Hb: Hemoglobin; LDH: Lactate dehydrogenase; CRP: C-reactive protein; PCI: Prophylactic cranial irradiation

to chemotherapy alone.[21] After meta-analysis results showing that survival was significantly improved with the addition of RT, studies were published examining the effect of optimal timing of RT and sequencing of chemotherapy on survival.[10-12] In the meta-analysis published by De Ruysscher, it was reported that 5-y OS improved with the initiation of thoracic RT within the first 30 days after the start of chemotherapy (OR: 0.64, 95% CI 0.44-0.92, p=0.02).[11] Thus, RT initiated with the first or second cycle of chemotherapy is superior to delayed RT. In our study, although RT was applied in the first 2 cycles in most of the patients, the survival benefit could not be shown statistically.

In the first studies, it is known that a total of 45 Gy RT was delivered in twice-daily fractions over 3 weeks.[22] However, it is not practical to apply twice a day in terms of clinical functionality. Therefore, when compared with conventional fractionation, studies have shown that doses of 60-70 Gy have similar efficacy to the hyperfractionated schedule.[23-25]. Two phase 3 randomized studies evaluating the efficacy of high dose once-daily thoracic RT showed no superiority over twice-daily accelerated thoracic RT, but both studies showed similar survival with dose escalation.[24,25]

Hypofractionated treatments that shorten the treatment day are quite indispensable. In this context, in a phase 2 randomized study comparing twice daily thoracic RT and 42 Gy once-daily thoracic RT for 3 weeks in both arms, the median OS was better in the twice-daily arm, although no statistically significant survival difference was demonstrated (p=0.61; 25.1 vs. 18.8 months).[26] In an another phase 2 randomized study comparing twice-daily thoracic RT with higher-dose hypofractionated thoracic RT, a significant difference in PFS was obtained with 65 Gy once-daily thoracic RT (p=0.031; 13.4 vs. 17.2 months).[27] Finally, a phase 2 randomized study compared 60 Gy twice-daily fractions for 4 weeks and 45 Gy twice-daily fractions for 3 weeks. At 2 years, in the 60 Gy arm, 74.2% of the patients were alive, while 48.1% were alive in the 45 Gy arm. It has been suggested that 60 Gy twice-daily thoracic RT can be an alternative

Table 3 Multivariate cox regression analysis for overall survival, progression-free survival, and local regional recurrence free survival

	OS		PFS		LRRFS	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
PCI						
+ versus -	2.11 (1.27-3.48)	0.055	-	-	-	-
Albumin						
≥35 versus <35	-	-	2.24 (1.12-4.48)	0.022	2.08 (1.06-4.08)	0.032

OS: Overall survival; PFS: Progression-free survival; LRRFS: Local regional recurrence-free survival; HR: Hazard ratio; CI: Confidence interval; PCI: Prophylactic cranial irradiation

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to the standard twice-daily schedule.[28] RT fractionation studies are still ongoing.[25] Today, one of these alternative schedules can be selected according to clinical functionality, physician, or patient preference. The conventional schedule with a median of 60 Gy was used in our clinic.

Tumor size and lymph node involvement are also among clinical factors known to be prognostic. According to the Veterans Affairs Lung Working Group in 1957, it was divided into two stages as limited and extensive-stage based on tumor volume involving a single radiation portal. This classification was found to be prognostic on survival. When analyzed by the International Association for the Study of Lung Cancer by restaging 8088 SCLC patients according to the TNM system, the effect of the TNM system on prognosis was demonstrated.[5,29] However, in our study, there was no difference because the majority of the patients were stage 3 according to the 8th edition of AJCC.

Until today, laboratory parameters were also checked for prognosis, and Hb, LDH, and CRP values were found to be correlated with survival.[15,16,30-33] It is known that increased LDH and CRP values are associated with tumor burden, and low albumin level is one of the indicators of tumor-related cachexia and malnutrition.[30] In studies evaluating the prognostic effect of albumin, it is often combined with other inflammatory and nutritional parameters.[31-33] Zhou et al.[31] reported that the albumin/globulin ratio was a predictive factor for OS, Yang et al.[32] reported that Hb, albumin, lymphocyte, and platelet score was an independent prognostic factor for OS, and Hu et al.[33] showed that advanced lung cancer inflammation index affects survival. In our study, no relationship was found between anemia, LDH, and CRP and survival, but it was shown that hypoalbuminemia negatively affects PFS and LRRFS.

Limitations of the Study

Despite the long duration of the study, the small number of patients who met the study criteria and the fact that it was a single-center study can be said to be the limitations of the study. Another is that the majority of patients in the study were at an advanced stage according to AJCC, which may have resulted in shorter expected survival times than in other studies. The inability to show a relationship between survival and factors known to be prognostic may be due to the small number of patients included in the study and the high number of patients with advanced stages.

CONCLUSION

In our study, the addition of PCI improved survival in patients with limited-stage SCLC who responded to primary therapy in univariate analysis. There was a trend on survival with PCI, but failed to show an association with OS in multivariate analysis. The decrease in neurocognitive functions due to PCI is beyond the scope of our study, but it should be applied to all patients knowing that this concern can be relieved with alternative methods instead of avoiding PCI. In addition, the decrease in albumin levels may also be important in terms of prognosis.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the University of Health Sciences, Samsun Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (no: 2021/20/15, date: 15/12/2021).

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