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Prognostic Value of Serum Lactate Dehydrogenase (LDH) Levels in Small Cell Lung Cancer Patients Receiving Thoracic Radiotherapy and Prophylactic Cranial Irradiation

Toraks Radyoterapisi ve Profilaktik Kraniyal Işınlama Alan Küçük Hücreli Akciğer Kanseri Hastalarında Serum Laktat Dehidrogenaz (LDH) Düzeylerinin Prognostik Değeri

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ABSTRACT

Objective: Small cell lung cancer (SCLC) accounts for 15% of all lung cancers and is more aggressive than other types of lung cancer. In these cases, the most important prognostic factor is the presence of brain metastases. According to the National Comprehensive Cancer Network guidelines, prophylactic cranial irradiation (PCI) is a treatment option to prevent brain metastasis. However, brain metastases develop within four years in 45% of patients despite PCI. Therefore, it is important to identify predictive factors for brain metastases. Serum lactate dehydrogenase (LDH) levels have long been recognized as a prognostic factor in many cancer contexts. In this study, we aim to evaluate the relationship between serum LDH levels and intracranial progression-free survival (ICPFS) as well as overall survival (OS) in SCLC patients receiving PCI and thoracic radiotherapy (TRT).

Methods: This study evaluated 50 patients who underwent PCI and TRT for SCLC between July 2012 and April 2024. Pre-treatment serum LDH levels and maximum serum LDH (mLDH) levels were recorded during the study. An increased serum LDH level was defined as a value exceeding 346 IU/mL. The relationship between serum LDH levels, OS, and ICPFS was evaluated using Kaplan-Meier analysis.

Results: The median mLDH level was determined to be 346 IU/L. Of the total number of patients (n=50), 25 exhibited elevated mLDH levels. No differences were observed between patients with normal and elevated mLDH levels regarding their characteristics. The median ICPFS for the elevated and normal mLDH groups was 15 and 29 months, respectively (p=0.01). The median OS was 25 months in

ÖZ

Amaç: Küçük hücreli akciğer kanseri (KHAK) tüm akciğer kanserlerinin %15'ini oluşturur ve diğer akciğer kanseri türlerine göre daha agresiftir. Bu vakalarda en önemli prognostik faktör beyin metastazlarının varlığıdır. Bu nedenle profilaktik kraniyal ışınlama (PKI) KHAK için standart tedavidir. Ancak, PKI'a rağmen hastaların %45'inde dört yıl içinde beyin metastazı gelişmektedir. Bu sebeple beyin metastazları için öngörücü faktörlerin belirlenmesi önemlidir. Serum laktat dehidrogenaz (LDH) düzeyleri uzun zamandır birçok kanserde prognostik bir faktör olarak kabul edilmektedir. Bu çalışmada, PKI ve torasik radyoterapi (TRT) uygulanan KHAK hastalarında serum LDH düzeyleri ile intrakraniyal progresyonsuz sağkalım (IKPFS) ve genel sağkalım (GS) arasındaki ilişkiyi değerlendirmek amaçlandı.

Yöntemler: Bu çalışmada, Temmuz 2012 ile Nisan 2024 tarihleri arasında KHAK nedeniyle PKI ve TRT uygulanan 50 hasta retrospektif olarak taranmıştır. Tedavi öncesi serum LDH düzeyleri ve çalışma sırasındaki maksimum serum LDH (mLDH) düzeyleri kaydedilmiştir. Artmış serum LDH düzeyi 346 IU/mL'yi aşan bir değer olarak tanımlanmıştır. Serum LDH düzeyleri ile GS ve IKPFS arasındaki ilişki Kaplan-Meier analizi kullanılarak değerlendirilmiştir.

Bulgular: Ortanca mLDH düzeyi 346 IU/L olarak belirlenmiştir. Toplam hasta sayısının (n=50) 25'inde mLDH düzeyi yüksekti. Normal ve yüksek mLDH düzeylerine sahip hastalar arasında özellikleri açısından herhangi bir fark gözlenmemiştir. Yüksek ve normal mLDH grupları için medyan IKPFS sırasıyla 15 ay ve 29 aydı (p=0,01). Ortanca GS, yüksek ve normal mLDH grupları için sırasıyla 25 ay ve ulaşılamadı (p=0,034).

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ABSTRACT

the elevated mLDH group and was not reached in the normal mLDH group (p=0.034). In the multivariate analysis, only mLDH levels were independently associated with OS (hazard ratio: 3.92; 95% confidence interval: 1.15-13.3; p=0.02).

Conclusion: Serum mLDH levels during TRT and PCI predict intracranial progression and survival in SCLC patients, helping identify at-risk patients who may benefit from aggressive treatment.

Keywords: Small cell lung cancer, lactate dehydrogenase, prophylactic cranial irradiation

ÖZ

Çok değişkenli analizde, yalnızca mLDH düzeylerinin bağımsız olarak GS ile ilişkili olduğu bulunmuştur (HR 3,92; %95 GA: 1,15-13,3; p=0,02).

Sonuç: KHAK'lı hastalarda TRT ve PKI esnasında ölçülen mLDH düzeyleri intrakraniyal progresyon ve sağkalımı predikte eder.

Anahtar Sözcükler: Küçük hücreli akciğer kanseri, laktat dehidrogenaz, profilaktik kraniyal ışınlama

INTRODUCTION

Small cell lung cancer (SCLC) represents approximately 15% of all lung cancer cases (1). SCLC is a highly aggressive tumor type with a proclivity for metastasis (2). The two-year overall survival (OS) rate for limited-stage SCLC is 40%, while it is less than 10% for extensive-stage SCLC (3,4).

In SCLC, the most important prognostic factor is the presence of brain metastasis. At the time of diagnosis, 10% of SCLC patients present with brain metastasis (5), and approximately 50% of patients develop brain metastasis as the disease progresses. In cases of brain metastasis, the median OS is six months (6). In light of these considerations, prophylactic cranial irradiation (PCI) has emerged as a significant intervention strategy. A meta-analysis revealed that PCI provided a 5.4% improvement in three-year OS for SCLC patients (7). However, even with the administration of PCI, the likelihood of developing brain metastasis remains at 15% after three years and 45% after four years (8,9). Therefore, it is crucial to identify new factors that can aid in predicting the development of brain metastasis.

LDH regulates the conversion of glucose to lactic acid, and its elevated levels have been identified as an adverse prognostic factor in lung cancer cases (10). A subsequent study has shown that high levels of lactate dehydrogenase (LDH) are linked to decreased OS in lung cancer patients receiving whole brain radiotherapy (WBRT) (11).

In conclusion, it is hypothesised that maximum serum LDH (mLDH) levels during the study may help predict new brain metastases and survival in SCLC patients undergoing thoracic radiotherapy (TRT) and PCI.

MATERIALS AND METHODS

We identified a total of 50 patients with SCLC who underwent TRT and PCI in our department between July 2012 and April 2024. We recorded the stage at diagnosis, the systemic therapies administered, the characteristics of radiotherapy, pre-treatment LDH levels, and mLDH levels. It is recommended that patients receive brain magnetic resonance imaging (MRI) and thoracoabdominal computed tomography scans every three months during the first two years and then every six months thereafter. The intracranial progression-free survival (ICPFS) is defined as the interval between the pathological diagnosis and the onset of brain metastasis MR. This study was approved by the Ethics Committee of Gülhane Training and Research Hospital (approval number: 2025/128, date: 12.06.2025). Informed consent form was not obtained since it was a retrospective study.

Statistical Analysis

The statistical analysis was conducted using IBM SPSS version 25 software. The patients' characteristics were subjected to descriptive statistical analysis. The LDH level cutoff was determined according to a median value of 346 IU/L. A chi-squared test and a t-test were used to evaluate the differences in clinical characteristics between the normal and elevated mLDH groups. A Kaplan-Meier analysis determined any differences in OS and ICPFS based on mLDH values. Ultimately, the Cox proportional hazards model was utilized to identify the most significant prognostic factors.

RESULTS

Patients Characteristics

The patients' characteristics are summarized in Table 1. The majority of patients were male. The median age of the patients was 59 years (range 46-75). Eighty percent of patients were classified as Eastern Cooperative Oncology Group (ECOG) score 1. All patients underwent thoracic chemoradiotherapy and subsequently received PCI. The TRT dose was 45-60 Gray (Gy) in 25-30 fractions, and the PCI dose was 25 Gy in 10 fractions. Concurrent chemoradiotherapy was administered to 41 patients (82%), while 9 patients (18%) underwent sequential treatment. Fifty-two percent of patients completed six cycles of chemotherapy, with the majority receiving the cisplatin-etoposide regimen. No significant differences were observed between patients with mLDH levels of ≤346 IU/L and those with levels greater than 346 IU/L.

Patient Outcomes

The median follow-up period was 21.5 months (range 6 to 122 months). After treatment with TRT and chemotherapy, 34 patients (64%) exhibited a partial response, while 16 patients (36%) demonstrated a complete response. After TRT and PCI, 10 patients (20%) experienced intracranial failure. The median time to failure was 15 months (range 9-35 months). Of the 10 patients, eight were in the high mLDH group. The median ICPFS was significantly lower in the high mLDH group compared to the low mLDH group (15 months vs. 29 months, p=0.01). The relationship between mLDH levels and ICPFS is illustrated in Figure 1.

In the univariate analysis for ICPFS, only mLDH was identified as a significant factor. However, the multivariate analysis did not identify any significant factors. The results of the multivariate analysis for ICPFS are presented in Figure 2.

The median survival time was 39 months in the general population. Patients with high mLDH levels exhibited inferior OS compared to those with low mLDH levels (25 months vs. not reached, respectively, p=0.034). The relationship between mLDH levels and OS is illustrated in Figure 3.

In both univariate and multivariate analyses, only mLDH levels were identified as an associated factor with OS (hazard ratio: 3.92; 95% confidence interval, 1.15-13.3, p=0.02). No association was found between OS and sex, age, ECOG, smoking status, or chemotherapy regimen/cycles (Figure 4).

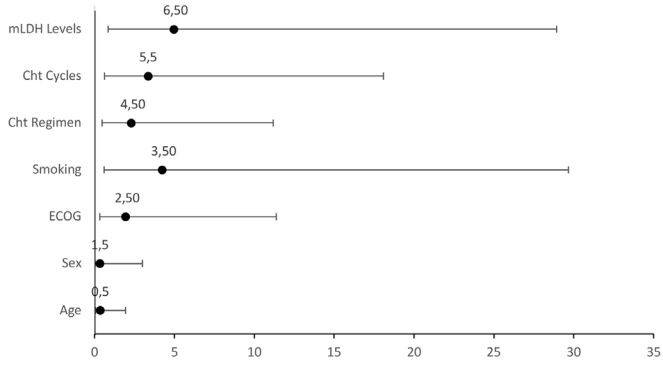

Figure 2. Multivariate analysis for ICPFS

LDH: Lactate dehydrogenase, Cht: Chemotherapy, ECOG: Eastern Cooperative Oncology Group, ICPFS: Intracranial progression-free survival

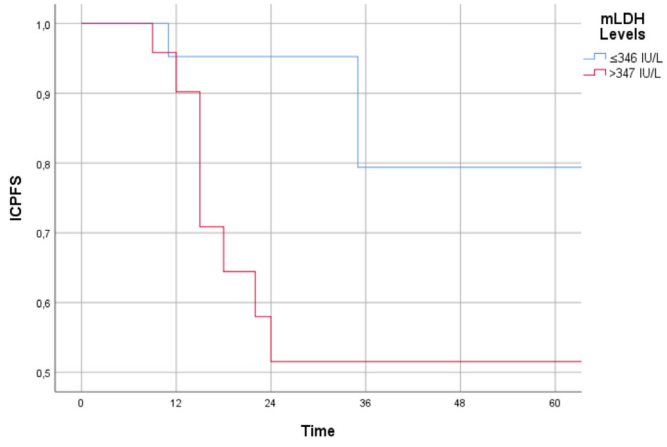

Figure 1. Kaplan-Meier curve of mLDH groups for ICPFS

mLDH: Maximum serum lactate dehydrogenase, ICPFS: Intracranial progression-free survival

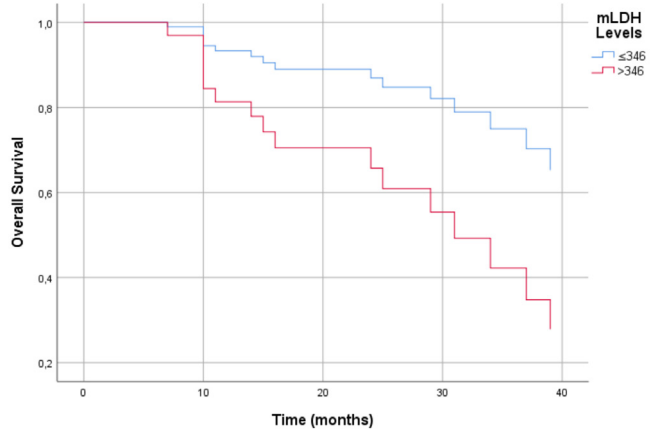

Figure 3. Kaplan-Meier curve of mLDH groups for OS.

mLDH: Maximum serum lactate dehydrogenase, OS: Overall survival

Table 1. Patients characteristics

Characteristic		Whole cohort	mLDH ≤346	mLDH >346	p-value
Age, years	≤59	26 (52%)	12 (48%)	14 (56%)	0.77
	>59	24 (48%)	13 (52%)	11 (44%)	
Sex	Male	39 (78%)	19 (76%)	20 (80%)	1
	Female	11 (22%)	6 (24%)	5 (20%)	
ECOG	0	8 (16%)	3 (12%)	5 (20%)	0.74
	1	40 (80%)	21 (84%)	19 (76%)	
	2	2 (4%)	1 (4%)	1 (4%)	
Smoking	Yes	33 (66%)	13 (52%)	20 (80%)	0.07
	No	17 (34%)	12 (48%)	5 (20%)	
Chemotherapy regimen	Cis-ETO	37 (74%)	17 (68%)	20 (80%)	0.51
	Carbo-ETO	13 (26%)	8 (32%)	5 (20%)	
Number of chemotherapy cycles	≤5	24 (48%)	15 (60%)	9 (36%)	0.67
	6	26 (52%)	10 (40%)	16 (64%)	

mLDH: Maximum serum lactate dehydrogenase, ECOG: Eastern Cooperative Oncology Group, Cis: Cisplatin, ETO: Etoposide, Carbo: Carboplatine

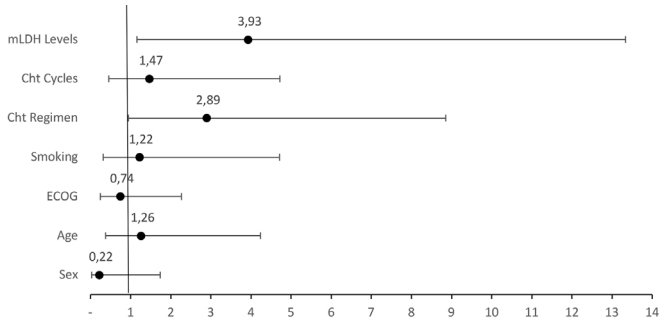

Figure 4. Multivariate analysis for OS.

mLDH: Maximum serum lactate dehydrogenase, Cht: Chemotherapy, ECOG: Eastern Cooperative Oncology Group, OS: Overall survival

DISCUSSION

SCLC is an aggressive cancer that has a strong tendency for brain metastasis (12,13). Therefore, the potential benefits of PCI have been discussed. In a meta-analysis published in 1999, Auperin et al. (7) found that PCI was associated with improved disease-free survival, OS, and a reduction in brain metastases. Subsequently, several studies corroborated these findings, establishing PCI as a standard of care for limited-stage SCLC (7,14-16). In extensive-stage SCLC, two pivotal studies have indicated that PCI may reduce the incidence of brain metastases. In the EORTC trial, a total of 286 patients with extensive stage SCLC were included. The incidence of symptomatic brain metastasis was significantly higher in the group that did not receive PCI (41.3% vs 16.8%, respectively). Patients in the PCI group exhibited significantly longer OS than those in the control group (6.7 months vs 5.4 months, p=0.003) (17). However, it should be noted that brain MRI is not mandatory for inclusion in the trial. As such, patients with brain metastases may be included, which could lead to a non-significant difference in OS. Subsequently, Takahashi et al. (18) conducted a trial in which brain MRI before randomization was mandatory. No significant difference in survival was observed between the PCI and control groups (11.6 months vs. 13.7 months, respectively; p=0.094). In conclusion, in limited stage SCLC, PCI reduces the incidence of brain metastasis and improves OS. However, PCI reduces the incidence of brain metastasis in extensive-stage SCLC, it doesn't improve OS.

The benefit of PCI in patients with extensive stage and very early stage (stage 1) disease remains unclear, and there is ongoing debate regarding the appropriate candidates for this procedure. Therefore, it is crucial to ascertain the risk of recurrence following PCI. LDH is a key enzyme in glycolysis. Since tumor cells primarily derive their energy through glycolysis, LDH plays a significant role in tumor growth, invasion, and metastasis (19,20). Research has shown that serum LDH serves as a predictor for various types of cancer, such as prostate, gynecological, gastrointestinal, and thoracic cancers (21-23). Furthermore, numerous studies have investigated lung cancer, especially SCLC. A meta-analysis of fourteen studies involving 4,084 patients indicated that elevated pretreatment LDH levels were significantly associated with decreased OS in lung cancer patients (10). In a study of patients with brain metastatic lung cancer who were treated with WBRT, pre-treatment LDH levels were associated with poor survival outcomes (11). Suzuki et al. (24) showed that high pre-treatment LDH levels were linked to a greater risk of brain metastasis. A study was subsequently conducted on patients with SCLC who had undergone TRT and PCI. This study identified the pre-treatment LDH levels and the maximum serum LDH levels during treatment as predictors of OS and ICPFS following TRT and PCI. The two-year OS and ICPFS rates were: 51.1% and 73.8% in the high mLDH group, and 74.2% and 91.7% in the low mLDH group, respectively (p<0.01 in both cases) (25).

The results of our research, indicate that elevated mLDH levels predict ICPFS and OS in patients undergoing treatment with TRT and PCI. Patients with elevated mLDH levels showed poorer OS and ICPFS outcomes compared to those with low mLDH levels (median OS: 25 months vs not reached months, respectively, p=0.034; median ICPFS: 15 months vs 29 months, p=0.01). These findings support previous research and confirm the link between LDH and prognosis. Given these findings, serum LDH levels can be used to predict the occurrence of brain metastasis and OS following PCI. This method allows for a more precise identification of patients who are likely to benefit from PCI.

Study Limitations

Our study has some limitations. Firstly, it is retrospective in design. Secondly, the sample size is small and the study is based on data from a single centre. Despite these limitations, it has demonstrated the prognostic value of LDH.

CONCLUSION

In conclusion, our findings indicate that the peak LDH levels during the treatment of patients with SCLC predict both intracranial failure and survival. The most significant limitation of this study is the relatively small sample size. Consequently, further research is needed to substantiate these findings.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Gülhane Training and Research Hospital (approval number: 2025/128, date: 12.06.2025).

Informed Consent: Informed consent form was not obtained since it was a retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.N.Ü., H.H., H.B., Concept: A.N.Ü., H.B., Design: A.N.Ü., H.B., Data Collection or Processing: A.N.Ü., H.H., Analysis or Interpretation: A.N.Ü., Literature Search: A.N.Ü., Writing: A.N.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

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