ARAŞTIRMA YAZISI / RESEARCH ARTICLE

SINIRLI EVRE KÜÇÜK HÜCRELİ AKCİĞER KANSERİ OLGULARINDA TEDAVİ ÖNCESİ İLERİ AKCİĞER KANSERİ ENFLAMSAYON İNDEKS DEĞERLERİNİN PROGNOSTİK ÖNEMİNİN ARAŞTIRILMASI

INVESTIGATION OF THE PROGNOSTIC IMPORTANCE OF PRE-TREATMENT ADVANCED LUNG CANCER INFLAMMATION INDEX VALUES IN LIMITED STAGE SMALL- CELL LUNG CANCERS

Emine Elif ÖZKAN, Zümrüt Arda KAYMAK

Süleyman Demirel Üniversitesi Tıp Fakültesi, Radyasyon Onkolojisi Ana Bilim Dalı

ÖZET

AMAÇ: İleri akciğer kanseri enflamasyon indeksi (İAKEİ), başta Küçük Hücreli Dışı Akciğer Kanseri (KHDAK)olmak üzere birçok kanserde yakın zamanda değerlendirilen enflamatuar indekslerden biridir. Ancak Küçük Hücreli Akciğer kanseri (KHAK) vakalarında aynı konudaki veriler azdır. Bu çalışmada, küratif amaçla tedavi edilen sınırlı evre KHAK hastalarında tedavi öncesi İAKEİ ile sağkalım arasındaki ilişkinin araştırılması amaçlandı.

GEREÇ VE YÖNTEM: Küratif amaçla torasik radyoterapi (RT) uygulanan 21 sınırlı evre KHAK hastası retrospektif olarak değerlendirildi. RT, 3D konformal (3DCRT) veya yoğunluk ayarlı RT (YART) teknikleri kullanılarak medyan 60 Gy olarak verildi. İAKEİ değerinin hesaplanmasında kullanılan değişkenler hastaların elektronik dosyalarından elde edildi. Hastalar düşük ve yüksek İAKEİ değeri olmak üzere iki grupta incelendi. Her iki grup için genel (GS) ve progresyonsuz sağkalım (PS) sonuçlarını elde etmek için Kaplan Meier sağkalım analizi kullanıldı. Cox regresyon testi ile tek değişkenli ve çok değişkenli analiz yapıldı.

BULGULAR: Medyan 26 (5,16-70,6) ay takip süresi sonunda 5 hasta halen hayattadır. Lokal ve uzak nüks oranları sırasıyla %47,6 ve %57,1 olarak bulunmuştur. Tüm kohortun PS ve GS'ı sırasıyla medyan 13,7 (5,16-82,76) ve 25,07 (6,9-85,59) aydı. İAKEİ<38 olan grupta medyan GS ve PS 22,4 ve 13,56 ay iken, İAKEİ>38 olan grupta sırasıyla 25,06 ve 13,7 idi (p=0,709 ve p=0,744). Tek ve çok değişkenli analizde incelenen diğer değişkenlerin hiçbiri istatistiksel olarak anlamlı bulunmadı (tek değişkenli analiz için p=0,059-0.930 ve çok değişkenli analiz için p=0.07-0.89).

SONUÇ: Çalışmamızda sınırlı evre KHAK olgularında tedavi öncesi İAKEİ değerinin sağkalıma prognostik etkisinin olmadığını saptadık. Sonuçlarımız ile önceki raporlar arasındaki uyumsuzluk, önceki çalışmalara kıyasla serimizdeki yüksek İAKEİ değerlerine ve sadece sınırlı evre KHAK hastalarının kaydına bağlanabilir.

ANAHTAR KELİMELER: Sınırlı evre küçük hücreli akciğer kanseri, İleri akciğer kanseri enflamasyon indeksi, Sağkalım

ABSTRACT

OBJECTIVE: Advanced lung cancer inflammation index (ALI) is one of the recently evaluated inflammatory indexes in many cancers, foremost Non-Small Cell Lung Cancer (NSCLC). However data in the same issue in Small Cell Lung Cancer (SCLC) cases is scarce. In this study the its aimed to investigate the correlation between pretreatment ALI and survival in limited stage SCLC patients treated with curative intend.

MATERIAL AND METHODS: Twenty-one limited stage SCLC patients who underwent definitive thoracic radiotherapy (RT) were retrospectively evaluated. RT was given as median 60 Gy using 3D conformal (3DCRT) or intensity modulated RT (IMRT) techniques. Variables used to calculate ALI value were attained from the electronical charts of the patients.   Patients were evaluated in two groups as low and high ALI value. Kaplan Meier survival analysis was used to achieve overall (OS) and progression free survival (PFS) results for both groups. Univariate and multivariate analysis were done by Cox regression test.

RESULTS: Five patients are alive after median 26 (5,16-70,6) months of follow up. Local and distant recurrence rates were found to be 47,6% and 57,1% respectively. PFS and OS of whole cohort were median 13,7 (5,16-82,76) and 25,07 (6,9-85,59) months respectively. Median OS and PFS of group with ALI<38 were 22,4 and 13,56 months where in the group with ALI >38, they were 25,06 and 13,7 respectively (p=0,709 ve p=0,744). None of the other variables investigated in uni and multivariant analysis were found to be statistically significant (p=0,059-0,930 for univariant analysis and p=0,07– 0.89 for mutivariant analysis).

CONCLUSIONS: In our study we detected that pretreatment ALI value have no prognostic effect on survival in limited stage SCLC cases. The discordance between our results and the previous reports can be attributed to high ALI values in our series compared to previous studies and enrolment of only limited stage SCLC patients.

KEYWORDS: Limitedstage small cell lung cancer, Advanced lung cancer inflammatiom index, Survival

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer worldwide which also accounts for a substantial part of cancer related deaths. Roughly 13% of lung cancer patients have small-cell histology (SCLC), which acts different in terms of biological behavior, treatment response, distant relapse and tendency to drug resistance (1, 2). Stage, age, performance status, smoking habit, are some of the reported prognostic variables for survival in SCLC patients (3 - 6). Interaction of inflammation and/or nutritional factors with cancer development and progression is also shown in recent studies (7). Systemic inflammation was found to have also an incontrovertible role in several cancer-related symptoms such as pain, anorexia, cachexia and debilitation (8). Increasing evidence is reported indicating utilization of C-reactive protein, Glasgow Prognostic Score, and neutrophil to lymphocyte ratio (NLR) for predicting prognosis in multiple malignancies, including colorectal, hepatopancreatic and lung malignancies (9 - 14). Advanced lung cancer inflammation index (ALI) which is one of the recently evaluated inflammatory indexes is first developed to validate the prognostic predictivity of systemic inflammation in non-small-cell lung cancer (NSCLC) (15). Low ALI has been reported to be correlated with worse OS in advanced NSCLC and esophageal squamous cell carcinoma (15, 16). However, the evidence is scarce about the prognostic value of this index in small-cell lung cancer (SCLC) (17). Our study aimed to investigate the relationship between the ALI and survival outcomes in limited stage SCLC (LS-SCLC) patients treated with curative intend.

MATERIAL AND METHOD

Treatment details and epidemiological data of 21 LS-SCLC patients who underwent definitive RT +/- concomitant chemotherapy in our Radiation Oncology Clinic between November 2011–April 2019 are retrospectively evaluated.

Patients with extensive stage SCLC, who were unable to complete the whole treatment, whose laboratory data are inaccessible were excluded. Radiotherapy (RT) was given to primary tumor + involved lymph nodes with 1.8-2 Gy fraction dose to a total dose of median 60Gy (60-66.6Gy) using 3D conformal (3DCRT) or intensity modulated (IMRT) RT techniques. Prophylactic cranial RT was given to whole brain after thoracic RT as 25Gy with 250 cGy fraction dose. Height, pretreatment weight, serum albumin (Alb), absolute neutrophil count and absolute lymphocyte count was attained from the complete blood count data in electronical charts of the patients. ALI value is calculated via [Body mass Index (BMI) x Serum Alb] / Neutrophil-lymphocyte ratio formula. Local and/or distant metastasis are identified from the control imaging modalities during follow up.

Ethical Committee

The study was approved by the Scientific Research Ethics Committee of Medical Faculty of Suleyman Demirel University (protocol code, 2020/53). All procedures were performed in terms of the ethical standards of the institutional research committee in alliance with the 1964 Helsinki declaration and its later amendments. Informed consent was waived owing to the retrospective nature of the study.

Statistical Analysis

For comparative statistical analysis patients are investigated as two groups (low and high) depending on ALI value. Overall (OS) and progression free survivals (PFS) of the two groups are evaluated via Kaplan Meier survival analysis.

Univariate and multivariate analysis are done by Cox regression. The Cox proportional hazard model was performed in multivariate analysis, and hazard ratios (HRs) estimated from the Cox analysis are reported as relative risks with corresponding 95% confidence intervals (CIs). Differences between groups were identified using the log-rank test. All tests were 2-sided, and $P < .05$ was considered to indicate statistical significance. All Statistical analyses were performed using Statistical Package for Social Sciences version 22.0 software (IBM, Armonk, NY).

Follow-Up: Overall survival was defined as the date of treatment to the date of death from any causes or last follow-up. The follow-up time was the beginning of diagnoses to end of last follow up. During the follow-up time, physical exami-

nation, complete blood count and computed tomography were carried out every 3 months.

RESULTS

All patients were male and median age was 61 (45-77) years. Patient characteristics according to 2 groups are given in **(Table 1)**.

Table 1: Patients' characteristics according to high and low ALI groups

| Characteristics		ALI ≤ 38 (n:11)	ALI > 38 (n:10)	Total (n:21)
Age	median	65	58	
	< 65	4 (36.4 %)	8 (80 %)	12 (57,1 %)
	≥ 65	7 (63,6 %)	2 (20 %)	9 (42,9 %)
T Stage	1	1 (9,1 %)	2 (20 %)	3 (14,3 %)
	2	0 (0 %)	2 (20 %)	2 (9,5 %)
	3	8 (72,7 %)	4 (40 %)	12 (57,1 %)
	4	2 (18,2 %)	2 (20 %)	4 (19 %)
N Stage	0	2 (18,2 %)	3 (30 %)	5 (23,8 %)
	1	0 (0 %)	2 (20 %)	2 (9,5 %)
	2	7 (63,6 %)	4 (40 %)	11 (52,4 %)
	3	2 (18,2 %)	1 (10 %)	3 (14,3 %)
ECOG	0	0 (0 %)	1 (10 %)	1 (4,8 %)
	1	7 (63,6 %)	6 (60 %)	13 (61,9 %)
	2	3 (27,3 %)	3 (30 %)	6 (23,6 %)
	3	1 (9,1 %)	0 (0 %)	1 (4,8 %)
BMI	median	24	28,7	
	< 26	7 (63,6 %)	2 (20 %)	9 (42,9 %)
	≥ 26	4 (36,4 %)	8 (80 %)	12 (57,1 %)
PCI	Yes	10 (90,9 %)	7 (70 %)	17 (81 %)
	No	1 (9,1 %)	3 (30 %)	4 (19 %)

All but 1 patient was given concomitant cisplatin etoposide chemotherapy. PCI was performed in 17 (81%) patients. After 26 (5.16-70.6) months of median follow up, 5 patients were alive. Local and distant recurrence were seen in 10 (47.6%) and 12 (57.1%) patients respectively.

PFS and OS of the whole group were median 13.7 (5.16-82.76) and 25.07 (6.9-85.59) months respectively. As ROC curve revealed a nonsignificant result to determine a cut off value for overall survival, median ALI value was accepted as cut off value. Calculated median ALI value before thoracic RT was 37.37 (9.83-81.79). Median OS and PFS of the group with ALI <38 were 22,4 and 13,56 months respectively. In the group with high ALI value, median OS and PFS were calculated as 25.06 and 13.7 months respectively. Although OS was higher in the group with ALI >38; the difference between two groups in terms of OS and PFS was not statistically significant (p=0.709 and p=0.744 respectively).

Overall and progression free survival curves are seen in respectively **(Figure 1, 2)**.
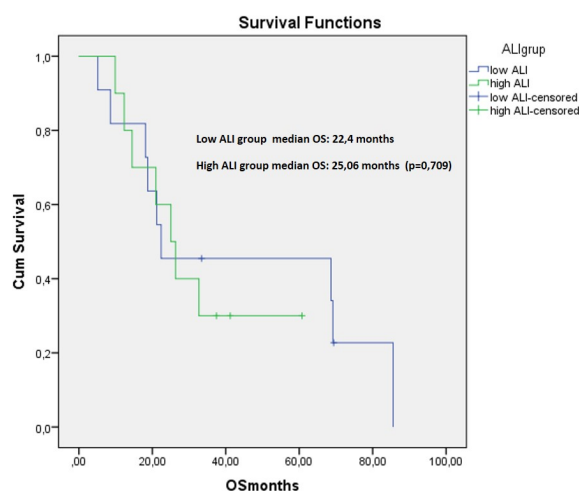
Figure 1: Overall survival curves of Low and High ALI Groups
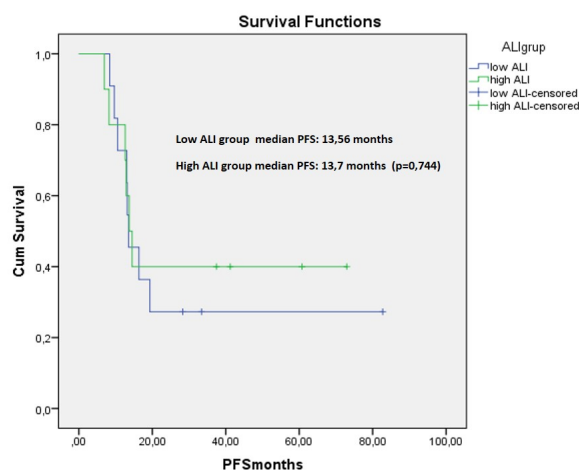
Figure 2: Progression free survival curves of Low and High ALI Groups

The effect of age, stage, BMI, ECOG and PCI were investigated with univariate and multivariate analysis and none of these prognostic factors were found to be statistically significant (p=0.059-0.930).

DISCUSSION

Several studies in the last 2 decades have called attention to association of inflammation and cancer (7, 18, 19). However, the mechanism of the inflammatory response in tumor is still a matter of debate. It may be secondary to tumor necrosis or local tissue damage caused by the tumor and healthy tissue interaction. Plenty of inflammatory cytokines are reported to indicate changes in inflammation. Prognostic significance of C-reactive protein (20) and NLR (21) in SCLC, colorectal cancer, hepatocellular car-

cinoma, and urinary cancer is reported, (9, 22-24). Hypoalbuminemia is also associated with inflammation, (25) and reported as a negative prognostic factor in many cancers (26). In patients with advanced NSCLC who underwent cisplatin-containing chemotherapy; decreased Alb levels were correlated with insufficient treatment response and survival (27). In addition, body mass index (BMI) was previously investigated as a predictor of OS benefit in many cancers, particularly colon cancer (28). Taking possible induction of a systemic inflammatory response with the carcinogenesis process into consideration, this should lead changes in several factors such as weight, Alb, NLR, and survival. Consequently, Jafri et al (15) developed ALI based on BMI, Alb and NLR. According to this definition, a low ALI value means decreased BMI, a lower Alb, and/or a high NLR which indicates poor prognosis and high systemic inflammation. BMI levels in the formula give clue about nutritional status of patients (29). Therefore, ALI was expected to provide a more comprehensive outlook the systemic inflammatory status of the patient to with a consequential powerful prediction of survival than any component alone included in the formula. In univariate analysis, we were not able to detect any association between poor OS and low ALI (P > 0,05). In their study on 466 SCLC patients, He et al. also found no significant difference with ALI levels in OS of limited stage subgroup (17). The authors attributed this result to low number of LD in low ALI group at diagnosis (n: 26) for statistically significant assessment.

In multivariable modeling, we investigated the prognostic significance of ALI with other clinical factors in SCLC patients, including clinical stage, PS, and LDH. According to reported results to date, ALI is suggested as a prognostic factor for survival in SCLC patients. Our study has several limitations, including being a single-center, retrospective designed investigation with a small sample size which restricts the generalizability our findings. The cutoff value for ALI was 38 which was the median of ALI values of whole sample and was higher than values selected in previous studies investigating the effect of ALI on survival. The ALI level which predicts prognosis in LS-SCLC with higher accuracy needs to be validated in prospective studies with larger sample of limited stage SCLC.

Regarding the proved importance of systemic inflammation in advanced lung cancer patients we investigated ALI as a prognostic indicator in limited SCLC patients. We were not able to demonstrate any significant effect of ALI on OS or PFS in our study. This contradictive result can be attributed to (1) high ALI values in our patients compared to previous studies in which cut off value was accepted as 18 – 19,5 (2) enrollment of only LS-SCLC patients. However, to best of our knowledge, this is the first study to investigate the prognostic role of ALI in only limited stage SCLC patients.

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