Evaluation of the Correlation Between Inflammatory Indices and Tumor Volume in Patients Received Chemoradiation

Kemoradyoterapi Uygulanan Hastalarda İnflamatuvar İndeksler ile Tümör Volüm Değişiminin İlişkisi

İsmail Beypınar[1], Fuzuli Tuğrul[2]

[1] Eskişehir City Hospital, Department of Medical Oncology, Eskişehir, Turkey

[2] Eskişehir City Hospital, Department of Radiation Oncology, Eskişehir, Turkey

ABSTRACT

Introduction: The utility of the inflammatory markers on definitive chemoradiation is worked on multiple cancers. Several studies had shown that tumor progression and prognosis were associated with immune status and nutritional condition. In this study, we aimed to elucidate the relationship between inflammatory markers and chemoradiation response in multiple cancer types in terms of tumor volume.

Methods: The patients who had been diagnosed with cancer and treated with concurrent chemotherapy and radiotherapy were included in the study. The patient characteristics, lymphocyte-neutrophil counts, hemoglobin, albumin and C-reactive protein levels, pathologic tumor subtype, stage of the disease, treatment modalities, tumor volumes, chemotherapeutic agents, and chemoradiotherapy outcome after the treatment were recorded.

Results: A total of 85 patients were enrolled in the study. The most frequent diagnoses were brain and rectal cancers following lung carcinomas. The most commonly used concurrent chemotherapy protocol was capecitabine. Sixty-seven percent of the patients have partial remission after chemoradiation, and 24.7% had complete remission. No correlations were observed between the volume reduction and inflammatory indexes. Also, the median alteration in tumor volume was not different between neutrophil to lymphocyte ratio (NLR) - prognostic nutritional index (PNI) high and low groups.

Conclusion: In this study, we found no relationship between tumor volume alteration and inflammatory markers. Although there was no association with the tumor volume change, NLR was a prognostic marker in patients who underwent definitive chemoradiation.

Key words: Cancer, Prognostic Nutritional Index, Neutrophil Lymphocyte Ratio, Prognosis, Chemoradiation

ÖZET

Giriş: Enflamatuar belirteçlerin tümörlerin kemoradyasyon yanıtı üzerindeki etkisi, birden çok kanser üzerinde çalışılmaktadır. Çok sayıda çalışma, tümör ilerlemesi ve prognozunun bağışıklık durumu ve beslenme durumu ile ilişkili olduğunu göstermiştir. Bu çalışmada farklı kanser tiplerinde, tümör hacmini değişimini açısından, farklı kanser tiplerinde inflamatuar belirteçler ile kemoradyasyon yanıtı arasındaki ilişkiyi araştırdık.

Yöntemler: Çalışmaya kanser tanısı yeterli olup eş zamanlı kemoterapi ve radyoterapi ile tedavi edilen hastalar dahil edildi. Hasta demografik özellikleri, lenfosit-nötrofil sayıları hemoglobin, albümin, C-reaktif protein düzeyleri, tümörün patolojik alt tipi, hastalığın evresi, tedavi modaliteleri, tümör hacimleri, kemoterapötik ajanlar ve tedavi sonrası kemoradyoterapi sonuçları kaydedildi.

Bulgular: Çalışmaya toplam 85 hasta dahil edildi. En sık tanılar akciğer kanserini takiben beyin ve rektal kanserlerdi. En sık eş zamanlı kemoterapi protokolü kapesitabin idi. Tam remisyon % 24,7 oranında saptanırken, hastaların yüzde altmış yedisinde kemoradyoterapi sonrası kısmi remisyon görüldü. Tümör boyut değişimi ile enflamatuar indeksler arasında hiçbir korelasyon gözlenmedi. Ayrıca, tümör hacmindeki medyan değişiklik nötrofil lenfosit oranı (NLO) - prognostik beslenme indeksi (PBI) yüksek ve düşük gruplar arasında farklı değildi.

Sonuç: Bu çalışmada, tümör hacmi değişikliği ile inflamatuar belirteçler arasında bir ilişki bulunmamıştır. Tümör hacminde azalma ile bir ilişki olmamakla birlikte, kesin kemoradyoterapi uygulanan hastalarda NLO prognostik bir belirteç olduğu sonucuna varılmıştır.

Anahtar Kelimeler: Kanser, Prognostik Beslenme İndeksi, Nötrofil Lenfosit Oranı, Prognoz, Kemoradyasyon

INTRODUCTION

The utility of the inflammatory markers on definitive chemoradiation is worked on multiple cancers. One of these cancers is lung cancer (LC) is the leading cause of cancer death worldwide. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) compose approximately 85% of the malign lung tumors (1, 2). Although rapid advances occur in lung cancer detection and treatment, the 5-year survival rates are still inconclusive (3). The second cancer in which

Corresponding Author: Dr. İsmail Beypınar, Eskişehir City Hospital, Department of Medical Oncology, Eskişehir, Türkiye
E-mail: ibeypinar@yahoo.com
Eskisehir Med. J. 2021; 2(1):23-28.
Received date:04.01.2021 Accepted date:09.02.2021
Authors: İsmail Beypınar (ORCID: 0000-0002-0853-4096), Fuzuli Tuğrul (ORCID: 0000-0001-9724-253X)

chemoradiation (CRT) is frequently used for curative intent is esophageal cancer (EC). CRT was proven to be more effective than chemotherapy (ChT) or radiotherapy (RT) alone in this indication (4, 5). The primary treatment way for head and neck cancers is CRT when curative surgery is not applicable. Nearly 70% of the patients have locally advanced disease at the time of diagnosis who are candidates for CRT (6, 7). Rectal cancer (RC) is also a frequent CRT indication in the neo-adjuvant setting. The response is found to be related to inflammatory markers (8).

Multiple studies had shown that tumor progression and prognosis are associated with immune status and nutritional condition (9, 10). The prognostic nutritional index (PNI), which is composed of serum albumin levels and circulating lymphocyte counts, can reflect both the immunological and nutritional status of cancer patients. (11) Multiple studies recently showed that PNI was correlated with prognosis in different types of human cancers such as colorectal, lung, gastric, and esophageal cancers (2, 12–16).

The systemic inflammatory response in many solid tumors has an essential role in development and progression (17). Some methods to measure systemic inflammation were established, such as PNI and neutrophil to lymphocyte ratio (NLR). These parameters were reported to correlate with poor prognosis in a variety of cancers, including NSCLC (18–22).

Several hypotheses speculated to understand this relationship between prognosis and lymphocyte counts. The lymphocytes are essential parts of the immune system, both controller and effector in response to tumor progression (23). Low lymphocyte counts were reported to correlate with decreased survival in cancer patients (24–26). Second, the PNI reflects both the patients' nutritional and immunological status, which could be associated with reduced survival (27). The third mechanism, the poor immune and nutritional course, may associate with postoperative morbidity and complications (28, 29).

In this study, we try to elucidate the relationship between inflammatory markers and chemoradiation response in multiple cancer types to alter tumor volume.

METHODS

Study Participants

In the retrospective cohort study, the archive records of patients diagnosed with cancer at Eskişehir City Hospital Radiation and Medical Oncology Departments between 2018 and 2020 were retrospectively analyzed. The patients who have an adequate cancer diagnosis and treated with concurrent chemotherapy and radiotherapy were included in the study. The patient characteristics, lymphocyte-neutrophil count, hemoglobin, albumin, C-reactive protein levels, pathologic subtype, stage of the disease, treatment modalities, tumor volumes, chemotherapeutic agents, and chemoradiotherapy outcome after the treatment were recorded. Also, the patients' PFS and OS were calculated. The exclusion criteria were lack of adequate cancer diagnosis and follow-up.

Radiologic Evaluation

The radiologic response evaluations were made via computed tomography (CT). The Response Evaluate Criteria for Solid Tumors (RECIST) method was used to measure disease response. Progressive disease (PD) was determined as the rise of new lesions or increase in primary tumor volume more than 20%; partial response (PR) was described as the decrease of at least 30% in the sum of the longest diameters of the target lesions; complete response (CR) was defined as the vanishing of all assessable lesions; the remaining patients who did not meet the criteria of PD or PR were considered as stable disease (SD) (30). The tumor volumes before and after CRT were calculated by the same radiation oncologist to prevent person-based differences. The response percent was calculated by the formula: 1- [(posttreatment tumor volume-pretreatment tumor volume)/ pretreatment tumor volume].

Ethics

The study was approved by Eskişehir Osmangazi University (01.09.2020 dated and 11 numbered decision) and carried out by the Declaration of Helsinki principles and all applicable regulations.

Statistical Analysis

The statistical analysis of the study performed with SPSS software (Statistical Package for

The Social Sciences, version 22.0, SPSS Inc, Chicago, IL). The Kolmogorov–Smirnov test was used to determine whether data conformed to a normal

Table 1. The features of the study population.

Features							
Age	Mean	Median					
(years)	64,2	67,0					
Gender	Male	Female					
N (%)	62 (72,9%)	23 (27,1%)					
Diagnosis	**Lung**	**Colon**	**Brain**	**H&N**	**GU**	**GIS**	**Other**
N (%)	15 (17,6%)	17 (20%)	17 (20%)	8 (9,4%)	13 (15,3%)	9 (10,6%)	6 (7,1%)
Chemotherapy Protocol	Cisplatin + Etoposide	Carboplatin + Paclitaxel	Capecitabine	Temozolomide	Platinum (only)	Unknown	
N (%)	2 (2,4%)	7 (8,2%)	20 (23,5%)	12 (14,1%)	7 (8,2%)	31 (36,5%)	
Response to CRT	CR	PR	SD	PD			
N (%)	21 (24,7%)	57 (67,1%)	6 (7,1%)	1 (1,2%)			
Markers	Hemoglobin	Neutrophil	Lymphocyte	Platelet	Albumin	NLR	PNI
Mean value	12,68 (g/dl)	4250 (mm^3)	1410 (mm^3)	226000 (mm^3)	3,95 (g/dl)	6,28	47,3

Abb. H&N: Head and Neck, GU: Genitourinary, GIS: Gastrointestinal Non-colorectal, PR: Partial Remission, SD: Stabile Disease, PD: Progressive Disease

distribution. Descriptive data are presented as either means or median for continuous variables; frequencies and percentages are reported for categorical variables. Pearson X2 test is used to assessing the associations in categorical variables. Pearson correlation was used for the evaluation of the relation between numeric variables. Overall survival (OS) and progression-free survival (PFS) curves are estimated by the Kaplan-Meier product-limit method.

RESULTS

A total of 85 patients were enrolled in the study. The mean age of the participants was 64.2 years. Sixty-two of the patients were male, while 23 were female. The most frequent diagnoses were brain and rectal cancers following lung carcinomas. The most concurrent chemotherapy protocol was capecitabine. Sixty-seven percent of the patients have partial remission after chemoradiation following by 24.7% of complete remission. The mean tumor volume before and after chemoradiation was 6332 and 169mm3, respectively. The mean radiation dose was 5510 cGy. The features of the study population are summarized in Table 1. No correlations were observed between response percent and inflammatory indexes. Also, the median alteration in tumor volume was not different between NLR-PNI high and low groups. (p = 0.30; p = 0.91) The correlation of the general study population's response percent and individual diagnosis between PNI and NLR was shown in Table 2. No difference was detected in median NLR and PNI values according to the diagnosis (p = 0.50; p = 0.13). There was no difference in tumor response according to the RECIST criteria in median NLR and PNI values (p=0.32; p = 0.064). Although there are no correlations of tumor response percentage with NLR and PNI, NLR as a prognostic factor in terms of OS when cut-off determined as 3 in univariate analysis (p = 0.047) (Figure 1). The median OS was 29 months for NLR high group while not reached for the low group. PNI had no predictive power when the cut-off value considered 50 (p = 0.26). None of the variables had prognostic effects on multi-variate analysis.

Table 2. The correlation between the response percent and PNI and NLR in the general population and according to diagnosis

Population	**PNI (co-eff)**	**p-value**	**NLR (co-eff)**	**p-value**
General	-0.018	0.86	0.165	0.13
Lung	-0.27	0.31	0.31	0.25
Colon	0.10	0.69	0.007	0.97
Brain	-0.21	0.41	0.27	0.28
H&N	-0.43	0.28	0.13	0.74
GIS	0.33	0.37	-0.20	0.60
GU	0.40	0.89	0.07	0.79
Other	0.63	0.17	-0.14	0.78

Abb. H&N: Head and Neck, GU: Genitourinary, GIS: Gastrointestinal Non-colorectal, Co-eff: Correlation Coefficient

DISCUSSION

In this study, we found no relationship between tumor volume alteration and inflammatory markers. Although no there was no relationship with decreased tumor

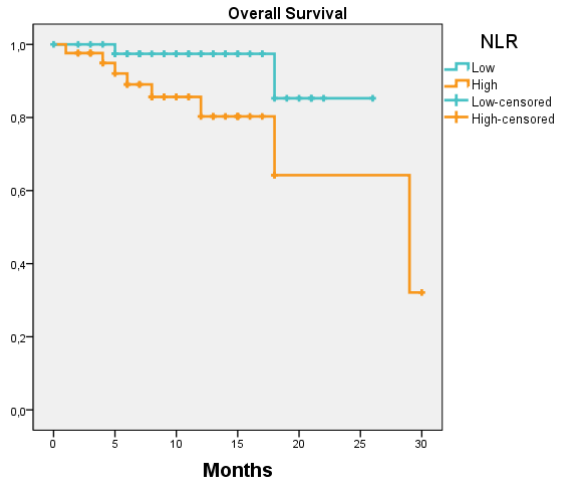

Figure 1. The Kaplan-Meier curves of NLR in the study group.

volume, NLR was a prognostic marker in patients who underwent definitive chemoradiation.

Although various studies investigated the prognostic effect of the inflammatory markers in cancer treatment, there are still controversial results among different cancer types, treatment modalities, and stages. In EC patients who received CRT in the front-line setting in patients with stage II-III, NLR was shown to be a dynamic and robust predictor for pathologic response rate, DFS, and OS (31). Although this study evaluated the inflammatory parameters periodically during treatment, our study had used the pre-treatment parameters. NLR was shown to be prognostic at multiple cancer types treated with CRT (32). Gorphe et al. had reported the independent prognostic effect of NLR and hemoglobin levels in oropharyngeal cancer in Human Papilloma Virus 16 positive patients. These patients had locally advanced disease and treated with CRT (33). In contrast, The relationship between elevated NLR or the other inflammatory markers and tumor volumes were not studied enough. Pre-treatment parameters assessed in patients who received CRT showed to be useful in anticipating the pathological outcome for rectal cancer (34). In a different study, post-CRT NLR was shown to be a prognostic factor in nasopharyngeal carcinoma. This study had a very high cut-off value for NLR as 7.5. (35). Although no correlation was observed between inflammatory markers and alteration of tumor volume with treatment, NLR had a prognostic effect on the study population. This effect of NLR may be independent of the tumor response in volume. In a study performed on EC in patients receiving CRT, the baseline tumor length was different among NLR groups. Although multi-variate analysis showed NLR was an independent prognostic factor in this study, only one-dimension tumor volume may not be adequate to evaluate these effects (36).

Tong et al. investigated the inflammatory markers in lung cancer and compared the prognostic power of NLR, PNI, and serum inflammatory index (SII) in locally advanced disease. Although SII was confirmed to be a more potent prognostic factor than PNI in this study, some other studies did not prove the effect of NLR and PNI for CRT response in both NSCLC and SCLC (37, 38). Our research found no prognostic impact of the PNI in patients who received chemoradiation in different disease types, including lung cancer.

Our study contained locally advanced patients who had undergone chemoradiation differently than other studies. Although PNI reported to be a prognostic factor in other studies, our study showed otherwise. The small sample size of our study group may be the underlying cause of this result. Further studies investigating the prognostic impact of inflammatory markers on especially chemoradiation plus immunotherapy, may be elucidative in this area.

The study was designed retrospective, which made the quality of data limited. The study population was not uniform in terms of diagnosis, which did not make an organ-specific outcome. A high number of concurrent chemotherapy protocols was not known. The study population was heterogeneous and not specific for one histologic sub-group.

CONCLUSION

Our study may exclude the tumor volume detoriation in good prognosis in patients receiving chemoradiation. The physiopathological mechanisms responsible for this phenomenon may need further evaluation. More specific and larger prospective studies are still needed.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: No funding was taken for this study.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015 Jan-Feb; 65(1): 5-29.

2. Chen P, Wang C, Cheng B, et al. Plasma fibrinogen and serum albumin levels (FA score) act as a promising prognostic indicator in non-small cell lung cancer. Onco Targets Ther. 2017 Jun 21; 10: 3107-18.

3. Zeng Q, Xue N, Dai D, et al. A Nomogram based on Inflammatory Factors C-Reactive Protein and Fibrinogen to Predict the Prognostic Value in Patients with Resected Non-Small Cell Lung Cancer. J Cancer. 2017 Feb 25; 8(5): 744-53.

4. Yang H, Liu H, Chen Y, et al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. J Clin Oncol. 2018 Sep 20; 36(27): 2796-803.

5. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009 Feb 20; 27(6): 851-6.

6. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov; 68(6): 394-424.

7. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol. 2003 Jan 1; 21(1): 92-8.

8. Sun Y, Huang Z, Chi P. An inflammation index-based prediction of treatment response to neoadjuvant chemoradiotherapy for rectal mucinous adenocarcinoma. Int J Clin Oncol. 2020 Jul; 25(7): 1299-307.

9. Candido J, Hagemann T. Cancer-related inflammation. J Clin Immunol. 2013 Jan; 33 Suppl 1: S79-84.

10. Sapienza C, Issa JP. Diet, Nutrition, and Cancer Epigenetics. Annu Rev Nutr. 2016 Jul 17; 36: 665-81.

11. Demir H, Beypınar İ, Baykara M. The Effect of the Prognostic Nutritional Index on Chemoradiotherapy Response in Lung Cancer. J Oncol Sci. 2020; 6: 96–102.

12. Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi. 1984 Sep; 85(9): 1001-5.

13. Hirahara N, Tajima Y, Fujii Y, et al. Preoperative Prognostic Nutritional Index Predicts Long-Term Surgical Outcomes in Patients with Esophageal Squamous Cell Carcinoma. World J Surg. 2018 Jul; 42(7): 2199-208.

14. Hong S, Zhou T, Fang W, et al. The prognostic nutritional index (PNI) predicts overall survival of small-cell lung cancer patients. Tumour Biol. 2015 May;36(5):3389-97.

15. Nakatani M, Migita K, Matsumoto S, et al. Prognostic Significance of the Prognostic Nutritional Index in Patients with Recurrent Esophageal Squamous Cell Carcinoma. Nutr Cancer. 2018 Apr;70(3):467-473.

16. Sun K, Chen S, Xu J, et al. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2014 Sep;140(9):1537-49.

17. Yang Y, Gao P, Song Y, et al. The prognostic nutritional index is a predictive indicator of prognosis and postoperative complications in gastric cancer: A meta-analysis. Eur J Surg Oncol. 2016; 42: 1176–82.

18. Proctor MJ, Morrison DS, Talwar D, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: A Glasgow Inflammation Outcome Study. Br J Cancer. 2011; 104: 726–34.

19. Proctor MJ, Morrison DS, Talwar D, et al . A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. Eur J Cancer. 2011; 47: 2633–41.

20. Cannon NA, Meyer J, Iyengar P, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non-small-cell lung cancer. J Thorac Oncol. 2015; 10: 280–5.

21. Shimizu K, Okita R, Saisho S, et al. Prognostic nutritional index before adjuvant chemotherapy predicts chemotherapy compliance and survival among patients with non-small-cell lung cancer. Ther Clin Risk Manag. 2015; 11: 1555–61.

22. Kinoshita A, Onoda H, Imai N, et al. Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma. Br J Cancer. 2012; 107: 988–93.

23. Sheng J, Yang YP, Ma YX, Qin T, Hu ZH, Hong SD, Zhou T, Huang Y, Zhao HY, et al. Low Prognostic Nutritional Index Correlates with Worse Survival in Patients with Advanced NSCLC following EGFR-TKIs. PLoS One. 2016 Jan 19; 11(1): e0147226.

24. Rosenberg SA. Progress in human tumour immunology and immunotherapy. Nature. 2001; 411: 380–4.

25. d'Engremont C, Vernerey D, Pointet AL, et al. Additive value of pre-operative and one-month post-operative lymphocyte count for death-risk stratification in patients with resectable pancreatic cancer: a multicentric study. BMC Cancer. 2016 Oct 26; 16(1): 823.

26. Kobayashi N, Usui S, Kikuchi S, et al. Preoperative lymphocyte count is an independent prognostic factor in node-negative non-small cell lung cancer. Lung Cancer. 2012; 75: 223-7.

27. Saito H, Kono Y, Murakami Y, et al. Prognostic Significance of Pre- and Postoperative Lymphocyte Counts in Patients with Gastric Cancer. Dig Surg. 2019; 36: 137–43.

28. Chen XL, Xue L, Wang W, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: A retrospective cohort study. Oncotarget. 2015; 6: 41370–82.

29. Schwegler I, Von Holzen A, Gutzwiller JP, et al. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. Br J Surg. 2010; 97: 92–7.

30. Watanabe M, Kinoshita T, Tokunaga M, et al. Complications and their correlation with prognosis in patients undergoing total gastrectomy with splenectomy for treatment of proximal advanced gastric cancer. Eur J Surg Oncol. 2018; 44: 1181–5.

31. Peng Y, Li Z, Zhang S, et al. Association of DNA base excision repair genes (OGG1, APE1 and XRCC1) polymorphisms with outcome to platinum-based chemotherapy in advanced nonsmall-cell lung cancer patients. Int J Cancer. 2014; 135: 2687–96.

32. Sherry AD, Newman NB, Anderson JL, et al. Systemic inflammatory dynamics during chemoradiotherapy predict response, relapse, metastasis, and survival in esophageal carcinoma. J Surg Oncol. 2020; 121: 303–12.

33. Guthrie GJK, Charles KA, Roxburgh CSD, et al. The systemic inflammation-based neutrophil-lymphocyte ratio: Experience in patients with cancer. Crit. Rev. Oncol. Hematol. 2013; 88: 218–30.

34. Gorphe P, Chekkoury Idrissi Y, Tao Y, et al. Anemia and neutrophil-to-lymphocyte ratio are prognostic in p16-positive oropharyngeal carcinoma treated with concurrent chemoradiation. Papillomavirus Res. 2018; 5: 32–7.

35. Hodek M, Sirák I, Ferko A, et al. Neoadjuvant chemoradiotherapy of rectal carcinoma. Strahlentherapie und Onkol. 2016; 192: 632–40.

36. Ou D, Wang X, Wu M, et al. Prognostic value of post-radiotherapy neutrophil-to-lymphocyte ratio in locally advanced nasopharyngeal carcinoma. Strahlentherapie und Onkol. 2020; 196:252–61.

37. Cox S, Hurt C, Grenader T, et al. The prognostic value of derived neutrophil to lymphocyte ratio in oesophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol. 2017; 125: 154–9.

38. Tong YS, Tan J, Zhou XL, et al. Systemic immune-inflammation index predicting chemoradiation resistance and poor outcome in patients with stage III non-small cell lung cancer. J Transl Med. 2017 Oct 31; 15(1): 221.

Cite as: Beypınar İ, Tuğrul F. Evaluation of the Correlation Between Inflammatory Indices and Tumor Volume in Patients Received Chemoradiation. Eskisehir Med J. 2021; 2 (1): 23-28.