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Effect of Covid-19 Pandemic on Patients Undergoing Definitive Chemoradiotherapy

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Research Article

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ABSTRACT

Abstract

Lung cancer is frequently seen in patients who smoke, who are elderly, and who have more comorbid diseases. The risk of being affected by the Covid-19 pandemic is high in these patients. Here, we aimed to determine the effectiveness of the definitive chemoradiotherapy (CRT) in patients with non metastatic Non-Small Cell Lung Cancers (NSCLC) during the pandemic period. Patients with NSCLCs, between 2020-2022 were evaluated retrospectively. Treatment responses were evaluated and prognostic factors were investigated. Twenty-eight patients (70%) were men and twelve (30%) were women. Twenty-five (62.5%) patients had comorbidities. All of patients complated their treatments. Objective response rate was 72.5%. Respectively, 72.5% of patients had partial response, 27.5% of patients had stable disease. 92.5% of patients had a reduction in primary tumor, 42.5% had lymph nodes and 75% had a reduction in stage. Seven (17.5%) patients developed Covid-19. Passing a Covid-19 was decreased survival (p=0.012). In conclusion; High response rates have been obtained with CRT treatment applied to NSCLC patients during the Covid-19 pandemic period. Covid-19 infection significantly reduced survival in NSCLC patients receiving definitive CRT.

Keywords: Covid-19, lymph node reduction, chemoradiotherapy, stage reduction

Covid-19 Pandemisinin Definitif Kemoradyoterapi Gören Hastalar Üzerinde Etkisi

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ÖZ

Akciğer kanseri, sigara içen, yaşlı ve komorbid hastalığı fazla olan hastalarda sık görülmektedir. Covid-19 pandemisinden etkilenme riski bu hastalarda yüksektir. Çalışmamızda metastatik olmayan Küçük Hücreli Dışı Akciğer Kanserli (KHDAK) hastalarda pandemi döneminde definitif kemoradyoterapinin (KRT) etkinliğini değerlendirmeyi amaçladık. 2020-2022 yılları arasında KHDAK'li hastalar retrospektif olarak değerlendirildi. Tedaviye yanıtları incelendi ve prognostik faktörler araştırıldı. Hastaların 28'i (%70) erkek, 12'si (%30) kadındı. Yirmi beş (%62.5) hastanın komorbiditesi vardı. Hastaların tamamı tedavilerini tamamlayabildi. Objektif yanıt oranı %72,5 idi. Sırasıyla hastaların %72,5'inde kısmi yanıt, %27,5'inde stabil hastalık elde edildi. Hastaların %92.5'inin primer tümör boyutlarında, %42.5'inin lenf nodlarında ve %75'inin evrelerinde azalma saptandı. Yedi (%17.5) hastada Covid-19 enfeksiyonu gelişti. Covid-19'u geçirilmesi sağkalımı azaltıyordu (p=0.012). Sonuç olarak; Covid-19 pandemi döneminde, KHDAK hastalarına uygulanan KRT tedavisi ile yüksek yanıt oranları elde edilmiştir. Definitif CRT alan KHDAK hastalarında Covid-19 enfeksiyonu geçirilmesi sağkalımı önemli ölçüde azaltıyordu.

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Anahtar sözcükler: Covid-19, lenf nodu küçülmesi, kemoradyoterapi, evre küçülmesi

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Introduction

Lung cancer is very common in men and women and is quite mortal [1]. Since March 2020, Türkiye has been struggling with coronavirus disease (Covid-19) [2]. Death occurs in approximately two percent of cancer patients. Most of the deaths in the Covid-19 epidemic were patients over 60 years of age and with comorbidities [3]. Lung cancer patients are among the groups at high risk in Covid-19 pandemic. Because cancer patients are mostly elderly, immunosuppressive individuals with multiple comorbidities. Our primary aim in this study was to determine the efficacy of definitive chemoradiotherapy (CRT) treatments in non-metastatic non-small cell lung cancers (NSCLCs) during the Covid-19 pandemic period.

Method

Patients with non-metastatic NSCLC's who applied to the Bursa City Hospital between 2020 and 2022 were evaluated for inclusion in to the study. Study was carried out in accordance with the Declaration of Helsinki, data usage permission was obtained. Bursa City Hospital Ethics Committee approval was obtained (Approval Date: 11.08.2021, Number:2021-14-7).

Criteria for inclusion; 1)age between ≥18-80 years, 2)diagnosed with non-metastatic NSCLC, 3)definitive CRT was performed on the first line for the primary tumor, 4)no active infection at the beginning of treatment.

Criteria for exclusion; 1)having a synchronous/metachronous tumor, 2)having immunosuppressive disease, 3)having Covid-19 infection at diagnosis.

Age, Eastern Cooperative Oncology Group (ECOG) Performance status, comorbidities, smoking status, Covid-19 transmission status, tumor histology were examined. American Joint Committee on Cancer eighth edition was used for Tumor (T), Node (N), Metastases (M) classification in clinical staging [4]. Treatment response was evaluated with Response Evaluation Criteria in Solid Tumors criteria [5]. Disease-Free Survival (DFS) was calculated as the time of diagnosis to recurrence or metastasis. Overall Survival (OS) was calculated as the time of diagnosis to death or last follow-up.

Simultaneus CRT regimen was weekly paclitaxel 45-50mg/m^2 and carboplatin AUC(2) through seven weeks. Consolidation chemotherapy regimen was two cylus paclitaxel 175-200mg/m^2+carboplatin AUC(5-6), after CRT [6]. Patients received 60-70Gy of definitive radiotherapy in two Gy fractions.

Patients were followed up every three months for two-three years with physical examination and laboratory techniques. Contrast-enhanced chest computured tomography (CT) was performed one month after definitive CRT, and *fluorodeoxyglucose* (*FDG*)-positron emission tomography (PET) was performed three months later.

Statistics: SPSS 22.0 (IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY) for Windows program was used. Descriptive statistics of evaluation results were given as numbers and percentages for categorical variables, median and interquartile range (IQR) for numerical variables. Survival rates were calculated by Kaplan Meier Analysis. Cox-regression analysis was performed to review risk factors and determine hazard ratios (HR). Confidence interval was determined as 95%, the statistical alpha significance level was accepted as $p < 0.05$.

Results and Discussion

A total of 40 patients were included in the study; 28 patients (70%) were male and 12 (30%) were female. Demographic, clinical, and tumor characteristics of patients are shown in Table-1. 25 (62.5%) of patients had comorbidities. ECOG performance status was 0-1 in 33 patients (82.5%), 2 or more in seven patients (17.5%). 16 (40%) patients were Stage IIIA and below, 19 (47.5%) were stage-IIIB, five (12.5%) were stage-IIIC. T1-2 was detected in 11 patients (27.5%), T3-4 in 29 patients (72.5%), N0-1 in 9 patients (22.5%), and N2-3 in 31 patients (77.5%). Covid-19 infection was detected in seven (17.5%) patients. None of our patients died due to Covid-19 infection. All patients were able to complete their treatment.

After the definitive CRT administration, 72.5% (29) of patients had partial response, 27.5% (11) of patients had stable disease. Objective response rate was 72.5%. No progressive disease was observed. 92.5% of patients had a reduction in primary tumor, 42.5% had lymph nodes and 75% had a reduction in stage. Primary tumor shrinkage was observed in 37 (92.5%) patients, lymph node reduction in 17 (42.5%) and stage reduction in 30 (75%) patients. During a median follow-up of 14.5 (9.3-20) months, recurrence was detected in 22 patients (55%) and metastasis was detected in 14 patients (35%). The median DFS was four months (95% CI 2.6-5.4) and the median OS was 20 months (95% CI 17.7-22.3). The one-year survival rate was 78.7% and two-year survival rate was 68.5%. In the Cox-regression analysis, getting Covid-19 infection was reduced survival (p=0.012).

Definitive concurrent CRT is the main treatment option in unresectable Stage-III NSCLC patients, who unsuitable for operation [7]. In our study, most of the patients had advanced stage (stage IIIB-C) and more nodal involvement (Node 2-3). During the pandemic, significant objective response, stage reduction and lymph node reduction rates were observed with definitive CRT. Survival was drastically reduced for those with Covid-19 infection. The limitations of our study are the retrospective nature and has limited patient group. Patients receiving maintenance immunotherapy could not be evaluated due to the lack of reimbursement in our country. Also, no information was given about the period of CRT treatment of Covid-19 infection and how it progressed.

Table 1. Demographic, clinical, and tumor characteristics of patients

Age (mean)	60.5±7.9	**Smoking**, (median) pocket/year	30 (5-45)
Gender, n(%)		**ECOG* Performance Status**	
Male	28 (70.0)	ECOG Performance Status 0-1	33 (82.5)
Female	12 (30.0)	ECOG Performance Status 2-3	7 (17.5)
Comorbidities, n(%)		**Body Mass Index**, n (%)	
Yes	25 (62.5)	<25	20 (50.0)
No	15 (37.5)	≥ 25	20 (50.0)
Tumor size, (cm) median	6.1 (5-7.5)	**Obective response rate**, n(%)	29 (72.5)
Tumor size, (cm) n(%)		**Histology**, n (%)	
< 3 cm	1 (2.5)	Adenocarcinoma	19 (47.5)
≥ 3 cm	39 (97.5)	Squamous cell carcinoma	19 (47.5)
		Mixt	2 (5)
Response rate, n(%)		**Passing Covid-19 infection**, n (%)	
Partial Response	29 (72.5)	Yes	7 (17.5)
Stable Disease	11 (27.5)	No	33 (82.5)
Lymph Nodes, n(%)		**Treatment after lymph nodes,** n(%)	
Node 0	5 (12.5)	N0	11 (27.5)
Node 1	4 (10.0)	N1	12 (30.0)
Node 2	25 (62.5)	N2	14 (35.0)
Node 3	6 (15.0)	N3	3 (7.5)
Clinical Stage, n (%)		**Chemoradiotherapy After Stage,** n(%)	
Stage I A, B	2 (5.0)	Stage I A, B	9 (22.5)
Stage II A	-	Stage II A	2 (5.0)
Stage II B	2 (5.0)	Stage II B	10 (25.0)
Stage III A	12 (30.0)	Stage III A	12 (30.0)
Stage III B	19 (47.5)	Stage III B	6 (15.0)
Stage III C	5 (12.5)	Stage III C	1 (2.5)
Recurrence or metastases, n (%)		**Treatment Completed**, n (%)	
Present	19 (47.5)	Yes	40 (100.0)
Absent	21 (52.5)	No	-
Disease Free Survival (month)	4 (2.6-5.4)[†]	**Overall Survival** (month)	20 (17.7-22.3)[†]

*ECOG: Eastern Cooperative Oncology Group, [†]Kaplan Meier test

Table 2. Cox regression analysis in patients undergoing definitive concurrent chemoradiotherapy

Variables	Univariate Analysis HR (95% CI)	p value
Age (years)		
≥65/<65	0.478 (0.165-1.384)	0.174
Gender		
Male/female	0.603 (0.219-1.665)	0.329
ECOG Performance Status*		
≥2/0–1	0.925 (0.263-3.256)	0.904
Comorbidities		
Presence/ Absence	0.664 (0.246-1.791)	0.419
Tumor Size	1.093 (0.855-1.399)	0.478
Getting Covid-19 Infection		
Yes/ No	4.035 (1.358-11.992)	**0.012**
Local Recurrence		
Presence/ Absence	1.564 (0.565-4.331)	0.389
Metastasis		
Presence/ Absence	1.712 (0.641-4.573)	0.284
Smoking. pocket/year	0.995 (0.976-1.014)	0.605
Body Mass Index		
≥25/<25	2.063 (0.746-5.702)	0.163
Objective Response Rate	1.718 (0.487-6.055)	0.400
Stage reduction after treatment	1.309 (0.371-4.613)	0.675
Presence/ Absence		
Post-treatment Stage-III	1.236 (0.461-3.312)	0.674
Presence/ Absence		
Pre-treatment Stage-III	0.888 (0.200-3.939)	0.876
Presence/ Absence		

*ECOG: Eastern Cooperative Oncology Group

Lung cancer is the leading cause of cancer-related death in both sexes [1]. The majority of NSCLC patients are advanced age, immunosuppressive and have excessive comorbidities and they are among the high-risk patients to be affected by the pandemic. In addition, during the pandemic period, simultaneous chemotherapy and radiotherapy treatment increase the risk of transmission of Covid-19 infection to patients, both during the patient's immune suppression and during hospital transportation. Most of our patients were male predominant patients who were older, smokers, and had comorbidities. Seventeen and a half percent of patients developed Covid-19 infection. Consistent with the literatüre, survival decreased in those who had Covid-19 [3].

In lung cancer, approximately one-third of patients are diagnosed at the regional stage. NSCLC survival improves with diagnostic, surgical, radiotherapy procedures, and medical treatments. Administering platinum-based chemotherapy sequentially or concurrently to thoracic irradiation resulted in a improvement of local control, metastasis-free and overall survival [8]. In the studies of Yılmaz U et al., complete and partial responses were obtained in 15 (18.2%) and 31 (37.8%) Stage IIIA and IIIB patients who underwent definitive CRT [9]. In stage III NSCLC, OS reaches 20-30 months with definitive CRT treatment [7]. In our study, the partial response was observed in 72.5% of patients and median OS was 20 months. The reason for this high rate in our study may be the inclusion of stage I and II patients, albeit small. In addition, all of our patients had completed their treatment.

Recently, immune checkpoint inhibitors have been applied in the treatment of advanced lung cancers. Concurrent CRT with maintenance immunotherapy in inoperable stage III NSCLC is an effective multimodal approach with two-year OS rates of 60 to 70% [10]. But there are controversial opinions about the use of immune check point inhibitors, which may cause cytokine release syndrome, in the Covid-19 pandemic [11]. In our study, immunotherapy could not be applied to our patients, response rates were high, survival rates and survival times were similar to patients who

underwent definitive CRT in the literature [1,10]. Completion of the treatment by all of our patients may explain the high treatment response rates. When applied by taking the necessary precautions during the Covid-19 pandemic period, CRT treatment has been used safely in patients and good responses have been obtained.

Conclusion

During the Covid-19 pandemic, definitive CRT is an effective and reliable method in NSCLC. Being infected with Covid-19 adversely affected survival. This patient group should be approached with a multidisciplinary team. Necessary precautions should be taken and followed closely against both the side effects of the treatments and the possibility of being affected by the pandemic.

Authors' Contribution:

EK; Conception and design of work, obtaining data of patients who were operated after neoadjuvant chemotherapy or patients who underwent definitive chemoradiotherapy, the analysis and interptretation of data revision of work, drafting the article or revising it critically for important intellectual content, final approval of the version to be published, aggreement to be accountable for all aspects of the work in ensuring that quetions related to the accuracy or integrity of any part of the work are approprately investigated and resolved.

AU; Conception and design of work, the analysis and interptretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be published, aggreement to be accountable for all aspects of the work in ensuring that quetions related to the accuracy or integrity of any part of the work are approprately investigated and resolved.

The manuscript has been read and approved by all the authors.

The requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

Ethics approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Bursa City Hospital (Approval Date: 11.08.2021, Number:2021-14-7).

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There is no conflict of interest between the authors.

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