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RESEARCH ARTICLE

Definitive Radiotherapy/Chemoradiotherapy Results in Geriatric Non-Small Cell Lung Cancer Patients with Multiple Comorbidity

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Abstract

Introduction: It was aimed to evaluate the definitive radiotherapy (RT)/ chemoradiotherapy outcomes in geriatric non-small cell lung cancer (NSCLC) patients with multiple comorbidities.

Methods: Patients who received RT 06.03.2019 and 24.10.2022 in XXX Hospital were analyzed retrospectively. The primary endpoints were RT compliance, acute adverse events (AAE), completeness of treatment. The secondary endpoints were overall survival (OS), disease-free survival (DFS).

Results: The results of 62 patients who received definitive RT/CRT were analyzed. Median follow-up time was 16 (2-55) months. The median age of the patients was 75(70-89) years. The median number of comorbidities was 3(2-6). Thirty-seven (59.7%) patients received concurrent chemotherapy (CRT);12(19.4%) patients received induction chemotherapy. One patient (1.6%) could not complete the RT and RT was interrupted in 6 (9.7%) patients. RT interruption was more common in patients with cerebrovascular disease (CVD) (p=0.002; OR5.5; CI %954,3-7). AAE were noted in 20 (32.3%) patients and AAEs increased with CRT (p=0.006; OR 6.2;95%CI1.5-24.4). Eighteen (29%) patients relapsed, 11(17.7%) of relapses were locoregional while 7 (11.3%) were distant. Median DFS was 12 (range1-50) months. Significantly higher DFS was observed in patients with squamous cell cancer (SCC) (p=0.021; HR 2.8;95%CI1.12-7.18). Thirty-three (53.2%) patients have died. Twenty-seven (81.8%) patients died without relapse, 6(17.2%) died after relapse. Median OS was 14 (2-50) months. Patients who interrupted RT had lower OS (p=0.003; HR5.96;95%-CI2.23-15.9). Patients with 3≥ comorbidities had lower OS (14 vs10 months) (p=0.053; HR2.3;CI95%0.98-5.8).

Conclusion: Definitive RT/CRT is an effective treatment with acceptable toxicity in geriatric NSCLC patients with multiple comorbidities.

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Introduction

According to GLOBOCAN 2020 statistics, an estimated 2,206,771 patients were diagnosed with lung cancer (LC) and 1,796,144 people die due to lung cancer.[1] The world population is aging, and more geriatric patients are refering oncology clinics. Consequently, an increase in lung cancer in the geriatric population is predicted.[2,3] However, treatment approaches are mostly based on studies of non-geriatric patient groups. It is an important problem that the treatment protocols obtained by excluding the geriatric patient group are applied directly to geriatric patients.[4]

In non-small cell lung cancer (NSCLC) patients, surgery is in the foreground in the early stage, while chemoradiotherapy (CRT) is indicated in locally advanced stages. Radiotherapy (RT) is an important part of local treatment in patients who are medically and surgically inoperable.[4] In elderly cancer patients with comorbidities who are not suitable for systemic therapy or surgery, radiotherapy is an effective treatment that can be used for both palliative and curative purposes.[5-8] CRT is a more effective treatment than only RT in this patient group, but it also causes a significant increase in advers effects.[9] It is important to consider the benefit/harm balance in the treatment decision.

The patient's chronological age should not be the only parameter for geriatric – fragile patient identification. In addition to chronological age, comorbidities, polypharmacy, functional status, life expectancy, psychological and mental status should also be evaluated.[10,11] Although the available data are limited, it has been reported that standard treatments are well tolerated, and oncologic outcomes are similar in elderly patients with good general condition.[12] There is no standard treatment approach in geriatric cancer patients with comorbidities, clinicians determine the treatment schemes according to the patient's condition and the extent of the disease. Evaluation of every geriatric patient admitted to the oncology clinic with geriatric scales and evaluation of these results together with oncological outcomes can guide the determination of treatment protocols.[13] Clearly, studies are needed for more standardized approaches. Patients should be evaluated from many aspects and clinics should routinely establish a scoring system for every geriatric patient.[12]

In this study, definitive RT/CRT results in NSCLC patients over 70 years of age and with at least 2 internal comorbidities were analyzed. It was aimed at evaluating the parameters affecting the tolerance of RT therapy and oncologic outcomes in geriatric NSCLC patients with multiple comorbidities.

Material and Methods

Geriatric patients who received curative dose RT with the diagnosis of NSCLC between 01.01.2019 and 30.12.2022 in the XXX Clinic of XXX Hospital were analyzed retrospectively. Patient files, dose volume histograms and medical records from electronic systems were used to obtain data. Patient demographics, complaints, radiological and pathological results, treatment details, acute adverse effects, recurrence status and final status were noted. Staging was performed according to American Joint Committee on Cancer (AJCC) ver 8., Common Terminology Criteria for Adverse Events (CTCAE) ver. 5 was used for acute adverse effect assessment.

Patient Selection

Patients with a diagnosis of NSCLC with pathological evidence, at least two internal comorbidities, age> 70years, receiving RT for curative purposes, and ECOG 0-3 were included in the study. The patients who could not complete radiotherapy were also included in the study. Under 70 years of age, without pathological evidence, with one or no internal comorbidity, patients receiving palliative RT and ECOG 4 were excluded. Patients with relapse or who underwent RT for adjuvant purposes were also excluded from the study.

Primary and Secondary Endpoints of the Study

The geriatric group is considered fragile, clinicians avoid aggressive treatments due to toxicity concerns. The primary endpoints of the study were interruption and completion of RT and acute RT toxicities. The secondary endpoints of the study were the evaluation of overall survival (OS) and disease-free survival (DFS) in this patient group. The end date of RT was accepted as the start date for the overall survey and DFS. The endpoint for OS was the last control date for surviving patients and the exitus date for those who died. The endpoint for DFS was the date of first event for patients with relapse, the date of last control for patients without relapse.

Statics

SPSS ver. 26 was used to note and analyze the data in the study. The conformity of the variables to the normal distribution was evaluated with histogram, detrend blot and Shapiro Wilk test. Non-para-

metric tests were preferred since its did not fit the normal distribution. Kaplan Meier and log rank test were used for univariate survival analysis. The significance limit of the study was accepted as 0.05.

Results

The results of 62 patients who received RT for curative purpose between 06.03.2019 and 24.10.2022 in our clinic were analyzed. Median follow-up time from diagnosis was 16 (2-55) months. The median age of the patients was 75 (range 70-89) years and 54 (87.1%) patients were male; 9 (12.9%) patients were women. The median number of comorbidities was 3.[2-6] There was a history of malignancy in 6 (9.7%) patients. The most frequently preferred RT technique was intensity modulated radiotherapy (IMRT) (n=53; 85.5%). RT total dose was median 60 (range 50-66) Gy. Concurrent chemotherapy was applied to 37 (59.7%) patients and induction chemotherapy (ind-CT) was applied to 12 (19.4%) patients. Concomitant chemotherapy was also applied in all patients receiving induction chemotherapy. Twenty-one (33.9%) of patients received no induction or concurrent chemotherapy. Patient and treatment details were summarized in Table 1.

Table I. Patient and treatment details

Parameters		n	%
Gender	Female	8	12.9
	Male	54	87.1
Age	Median (range)	75 (70-89)	
Localisation	Right	35	56.5
	Left	27	43.5
Stage	1	10	16.1
	2	6	9.7
	3	36	58.1
	4	10	16.1
Pathology	SCC	48	77.4
	Adenocancer	14	22.6
Chemotherapy	Induction CT+C-RT	8	12
	Induction CT+RT	4	6
	CRT	29	46
	Only RT(without CT)	21	33
Number of Comorbid Diseases	Median (range)	2 (0-6)	
	2 comorbidities	17	27.4
	3 or more comorbidities	45	72.6
COPD	No	33	52.2
	Yes	29	46.8
CAD	No	32	51.6
	Yes	30	48.4
CVD	No	58	93.5
	Yes	4	6.5
Malignancy anamnesis	No	56	90.3
	Yes	6	9.7 Lymphoma 1 (1.6) Laryngeal cancer 2 (3.3) Colon Cancer 1 (1.6) Prostate Cancer 2 (3.3)
RT Technique	3D	1	1.6
	IMRT	53	85.5
	VMAT	2	3.3
	SRT	6	9.7
RT Total Dose	Median (range)	60 (50-66)Gy	
RT Interruption	Interrupted	6	9.7
	Not interrupted	56	90.3
RT Complete Status	Completed	61	98.4
	Not completed	1	1.6
Concurrent CT	Yes	37	59.7
	No	25	40.3
Induction CT	Yes	12	19.4
	No	50	80.6
Acute Adverse Effect	No	42	67.7
	Yes	20	32.3 Dysphagia 18 (29) Leukopenia 2 (3.3)
Recurrence	No	44	71
	Yes	18	29 Locoregional 11 (17.7) Distant 7 (11.3)
Last Status	Alive	29	46.8
	Ex	33	53.2

SCC: Squamous cell cancer; RT:Radiotherapy; CT: Chemotherapy; 3D: Conformal RT; IMRT: Intensity Modulated RT; VMAT: Volumetric arc RT; SRT: Stereotactic RT; COPD : Chronic obstructive pulmonary disease; CAD: Coronary artery disease; CVD: Cerebrovascular disease

Radiotherapy Tolerance

RT compliance of the patients was high. RT was interrupted in only 6 (9.7%) patients. The treatment interruption durations were as follows; 22 days, 21 days, 19 days, 9 days, 6 days and 5 days. The reason for the interruption was the deterioration of the general condition of the patients. There was no significant relationship between RT-interruption and gender (p=0.420); right and left primary (p=0.220); pathology (SCC vs adenocancer) (p=0.590); malignancy anamnesis (p=0.528); number of comorbidity(2 vs 3 and higher)(p=0.176), chronic obstructive pulmonary disease(COPD) (yes or no)(p=0.868), coronary artery disease (CAD) (yes or no)(p=0.099); stage (p=0.866); RT technique (p=0.770); applying CR

T (p=0.678); applying ind-CT (p=0.586) or RT total dose (0.638). RT was interrupted more frequently in patients with cerebrovasculary disease (CVD) (p=0.002; OR 5.5; CI %95 4.3-7). Treatment was interrupted in 3 of 4 patients with CVD.

Only 1 patient (1.6%) could not complete their treatment. The patient who could not complete the RT scheme was an 87-year-old T3N0 SCC male patient. This patient did not receive induction or concomitant CT. The patient, who was planned 60 Gy, did not continue the treatment due to deterioration of the general condition while at the 54 Gy. Local progression was observed at 14 months of follow-up. He died in the 21st month after RT.

Acute Adverse Effect Assessment

Acute adverse events were noted in 20 (32.3%) patients. The most common acute adverse effect was dysphagia, and it was seen in 18 (29%) of patients. There was no significant relationship between acute adverse effects and gender (p=0.705); right and left primary (p=0.544); pathology (SCC vs adeno) (p=0.495); stage (p=0.097) malignancy anamnesis (p=0.495); number of comorbidity (2 vs 3 and higher)(p=0.265); COPD (yes or no)(p=0.458); CAD (yes or no)(p=0.262); CVD (yes or no)(p=0.201); RT technique (p=0.150); applying ind-CT (p=0.591) or RT total dose (0.833).

Acute adverse events were observed in 45.9% of patients receiving concomitant chemotherapy and in 12% of patients who did not receive concomitant chemotherapy. Acute adverse events significantly increased with CRT (p=0.006; OR 6.2; 95% CI 1.5-24.4).

According to AJCC TNM staging nodal stage of the patients included in our study were as follows: N3: 14 patients, N2: 19 patients, and N0-1: 29 patients. Unexpectedly, it was observed that 2 of the N3 patients (14%) and 5 of the N2 patients (26%) started treatment with induction chemotherapy. Oligometastatic patients evaluated as M1 constituted 16% (n=10) of all patients.

DFS Analysis

During the follow-up period, 18 (29%) patients relapsed, and the disease was under control in 46 (73.1%) patients. While 11 (17.7%) of the relapses were locoregional, 7 (11.3%) were distant. Median DFS was 12 (range 1-50) months (Figure 1). There was no significant relationship between DFS and gender (p=0.665); right and left primary (p=0.417); malignancy anamnesis (p=0.848); number of comorbidity (2 vs 3 and higher)(p=0.215); COPD (yes or no)(p=0.063); CAD (yes or no)(p=0.081); CVD (yes or no)(p=0.241); stage (p=0.740); RT technique (p=0.102); RT interruption (p=0.448); applying CRT (p=0.564); applying induction CT (p=0.936) or RT total dose (p=0.052).

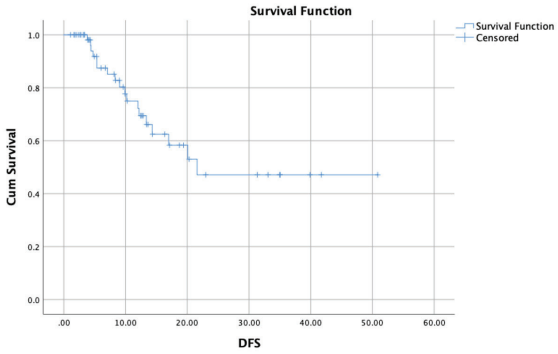

Fig.1. Disease free survey Kaplan Meier analysis

A significantly higher DFS was observed in patients with primary SCC who received definitive RT compared to adenocancer. The median DFS of SCC patients was 13 (range 1-41) months and it was 9 (range 1-50) months in adenocancer patients (p=0.021; HR 2.8; 95% CI 1.12-7.18)(Figure 2).

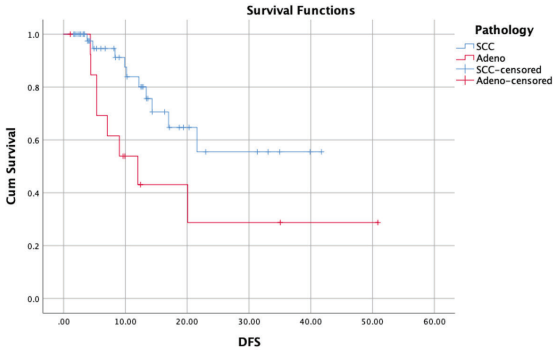

Fig.2. A significantly higher DFS was observed in patients with primary SCC than adenocancer.

OS Analysis

During the follow-up period, 33 (53.2 %) patients have died, 29 (46.8%) patients were alive. Of the 33 patients who died, 27 (81.8%) died without relapse, 6 (17.2%) died after disease relapse. Median OS was 14 (range 2-50) months (Figure 3). There was no significant relationship between OS and gender(p=0.393); right and left primary (p=0.412); pathology (SCC vs adenocancer) (p=0.602); stage (p=0.063); malignancy anamnesis (p=0.333); COPD (yes or no)(p=0.420); CAD (yes or no)(p=0.148); CVD (yes or no)(p=0.153);RT technique (p=0.191); applying CRT (p=0.065); applying induction KT (p=0.795) or RT total dose (p=0.055).

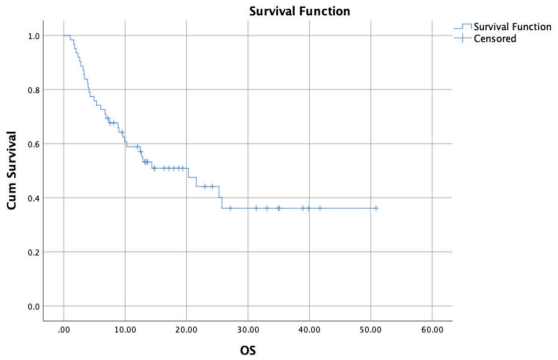

Fig. 3. Overall survey Kaplan Meier analysis

A significantly lower OS was observed in patients who interrupted RT (p=0.003; HR 5.96; 95% CI 2.23-15.9). Median OS was 15.4 (range 2-50) months in patients who did not interrupt RT and median OS was 4 (2-46) months in patients with RT interruption (Figure 4).

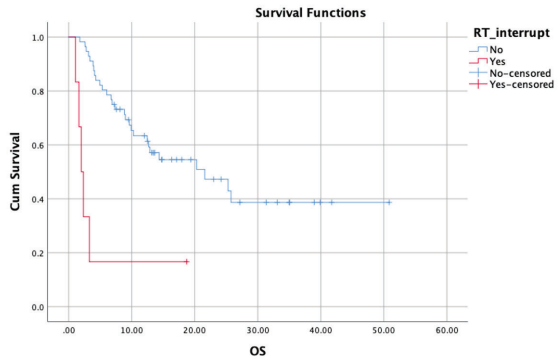

Fig.4. A significantly lower OS was observed in patients who interrupted RT compared to those who did not.

The relationship between the number of comorbidity and OS was close to the limit of significance (2 vs 3 and higher) (p=0.053; HR 2.3;CI95% 0.98-5.8). The median OS in patients with 2 internal comorbidities was 14 (range 3-39) months. The median OS value was 10 (range 1-50) months in patients with three or more comorbidities (Figure 5).

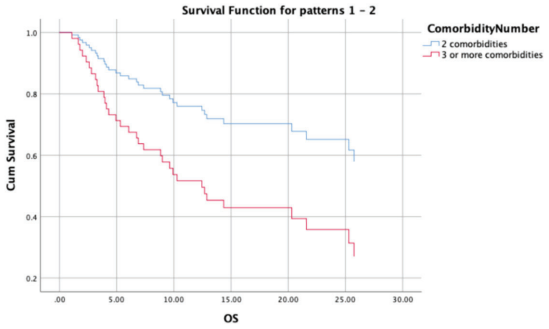

Fig.5. The relationship between the number of comorbidity and OS was close to the limit of significance (p0.053).

Discussion

Sixty-two geriatric patients with multiple comorbidities were analyzed. Treatment compliance of the patients was excellent, only 1 (1.6%) patient could not complete the RT scheme. RT was interrupted in only 6 (9.7%) patients. RT was interrupted more frequently in patients with CVD. Acute adverse events were significantly higher in patients receiving concomitant chemotherapy. No increase in acute adverse effects was observed in patients who received induction chemotherapy before concomitant CRT. There was a 4-month DFS difference in SCC patients compared to adenocancer, and this difference was significant (13 vs. 9 months). Patients who interrupted RT had dramatically lower OS (15.4 vs 4 months). OS was lower in patients with 3 or more internal comorbidities (14 vs 10 months) and the difference was close to the limit of significance (p=0.053).

Due to the changing demographic structure of the world, more geriatric patients are admitted to RT clinics. However, this patient group is underrepresented in clinical studies and is treated with a protocol that is not tailored to them. Considering lung cancer, comorbidities, which are more common with increasing age, may cause a decrease in RT tolerance.[12] The standard approach in early-stage NSCLC is surgery, and SBRT can be applied in patients who are not suitable for surgery. A pooled analysis of prospective randomized STARS and ROSEL studies showed improved survival with SABR than surgery in resectable patients, although not focusing on elderly patients.[14] Updated results of the STARS trial, published in 2021, stated that SABR is an effective short-term cu-

rative therapy with acceptable toxicity for frail or elderly patients, too.[15] In 772 patients with early stage I-II NSCLC (T1-T3N0M0) Brooks et al evaluated the effectiveness of SABR (50 Gy in 4 fractions or 70 Gy in 10 fractions).[16] While 442 of the patients were aged <75 years; 330 patients were aged ≥75 years. In this study, which had a median follow-up of 55 months, there was no significant difference between time-to-progression (p=0.419), lung cancer-specific survival (p=0.275), or toxicity (p=0.536) in the patient arm aged below 75 years and older. No patient ≥75 years of age experienced any grade 4 or 5 toxicity. In OS analysis, 1- and 3-year OS values were similar, but 5-year OS was lower in the advanced age group.[16] In the SEER-based study of Sigel et al, 6468 geriatric unresectable NSCLC patients who had undergone RT alone were analyzed. The OS contribution was observed with RT, but the patients had an increased risk of hospitalization for pneumonitis and esophagitis. These results suggest that the use of RT alone may improve outcomes in elderly patients with unresected stage III NSCLC. However, severe toxicity was significantly higher in the RT-treated group. They commented that the potential risks and benefits of RT should be carefully discussed with eligible elderly NSCLC patients.[17] In current study, the median follow-up period was 16 months and the median OS was 14 months. During the follow-up period, 33 (53.2 %) patients have died. Our remarkable result was that 27 (81.8%) of 33 patients died without recurrence. In our geriatric patient population with multiple comorbidities, a significant portion of our patients died while the disease was under control. Due to the retrospective nature of our study, long-term treatment adverse effects and the relationship between these adverse effects and the exact cause of death could not be reached. However, the high mortality rates that occur while the disease is under control clearly show that a treatment decision should be made considering the profit and loss balance, whether it is treatment-related or not.

Comorbidities are predicted as a very important determinant of lung cancer survival, and this importance is more pronounced in geriatric patients.[18] There are not enough studies to evaluate multiple comorbidities in geriatric NSCLC patients. One of the most interesting studies on the subject has been done by Cardia et al.[19] The results of 90 lung cancer (SCLC + NSCLC) patients over 70 years of age were evaluated in the study. In this study, groups were analyzed according to those with and without comorbidity. There was no significant difference in survival between the two arms.[19] Janssen-Heijnen et al evaluated the relationship between age, comorbidity and survival in NSCLC patients. In patients with comorbidities, despite less aggressive treatment, comorbidity seemed to have a negligible effect on survival of patients with lung cancer.[20] In the study of Fırat et al, 112 stage 3 NSCLC patients from 4 Radiation Therapy Oncology Group (RTOG) studies (RTOG 83-11, 84-03, 84-07, and 88-08 nonchemotherapy arms) were evaluated in terms of the relationship between comorbidity and survival.[21] In this study, comorbid diseases were evaluated with The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and Charlson scales. And they found that, comorbidities were defined as important independent prognostic factors in Stage III NSCLC.[21] Unlike other studies,[19,20] Fırat used a score that takes into account not only the presence or absence of comorbid disease, but also the number and severity of comorbid diseases.[21] Therefore, while comorbidity did not have a significant effect on survival in other studies,[19,20] it may have been significant in the study of Fırat et al.[21] It would be more accurate to evaluate the relationship between comorbidities and survival with scales that include the number, degree and severity of diseases. In our study, the number of diseases was evaluated, but a scoring that also evaluated the severity of the disease was not performed. According to our results, lower OS was observed in patients with three or more comorbidities. However, the number of patients in our study was small and the follow-up period was short. It is thought that this difference may become significant in larger series and longer follow-up.

RT interruption should not be acceptable unless necessary. The most common causes of RT interruption are public holiday, linak breakdown and treatment-resistant acute adverse events. It has been proven that prolonging the overall treatment time in many cancers such as cervical cancer, head and neck squamous cell carcinoma and anal squamous cell carcinoma adversely affects local control and survival.[22-24] There are limited studies evaluating the relationship between treatment interruption and survival in NSCLC patients. In these studies, it was observed that the prolongation of the treatment period worsened the local control and survival.[25-27] In the study

of Jeremic et al, the relationship between treatment interruption and oncologic outcomes was evaluated in NSCLC patients undergoing hyperfractionated RT (69.6 Gy, 1.2 Gy b.i.d.).[29] Patients with RT- interruptions had statistically significantly lower OS, local recurrence free survey (LRFS) and cause specific survival (CSS).[25] McMillan et al evaluated the relationship between prolonged radiation treatment and survival in NSCLC patient.[30] In this study, 14,154 patients were screened from The National Cancer Database, and the RT prolongation was observed in 6262 (44.2%). It was emphasized that prolongation of RT duration was an independent risk factor for OS in NSCLC patients and RT interruption should be minimized.[30] In this study, treatment was interrupted by approximately 10% of our patients. Like the literature, RT interruption resulted in a decrease in OS (15.4 vs 4 months). Another significant result of RT interruption is that it was observed more frequently in patients with CVD. Although RT interruption to treatment was observed in 75% of patients with CVD in our study, acute adverse effects, DFS and OS were not significantly affected. However, only 6.5% of our patients have a history of CVD. For a more accurate interpretation, the relationship between CVD and oncologic outcomes should be evaluated in larger series.

In patients with NSCLC who are scheduled for definitive RT, CRT improves oncologic outcomes compared to RT alone, while increasing adverse effects.[5,31,32] Especially because of cardiopulmonary comorbidities, patients are not suitable for systemic treatment. In this patient arm, sequential therapy is more appropriate than concurrent therapy, and the oncological results of sequential chemotherapy are better in geriatric patients compared to younger patients.[5,33] In the Japan Clinical Oncology Group studies, RT concomitant low-dose carboplatin was evaluated in geriatric patients. Confirmed the survival benefits of CRT in elderly patients with locally advanced NSCLC. No increase in late toxicity was observed with CRT compared to RT alone.[34-36] In this study, there was no patient arm who received sequential chemotherapy. Concurrent chemotherapy was applied to all 12 patients who received induction. A significant increase in acute toxicity was observed with concomitant CT, but the presence of induction did not cause an increase in RT toxicity.

SCC and adenocarcinoma are two distinct subtypes that differ in histology, anatomical localization and prognosis.[37] Adenocancer and SCC are also radiosensitive, although not as much as small cell lung cancer (SCLC).[38] Nomori et al evaluated CRT outcomes of adenocarcinoma and SCC.[36] More residual tumor, worse clinical and pathological responses were observed in adenocancer patients compared to SCC patients. In addition, recurrence-free survival was worse in adenocarcinoma patients, while OS was similar in both pathologies.[39] The results of our study are also in agreement with the results of Nomori et al. Higher DFS is observed after definitive RT in SCC patients compared to adenocancer. However, there was no significant difference in overall survival.

The study was single-center and retrospective. Because of its retrospective nature, geriatric examination or any geriatric scoring was not performed. The number of patients was low, the follow-up period was short, and long-term adverse effects could not be evaluated. Evaluation of immunological agents was not performed. A comparison of concurrent and sequential CRT could not be made. The exact cause of death could not be determined for every patient. Lastly, the number of diseases was evaluated, but a scoring that also evaluated the severity of the disease was not performed.

Conclusions

Definitive RT/CRT is an effective treatment with acceptable toxicity in geriatric NSCLC patients with multiple comorbidities. The treatment compliance of the patients is excellent. Higher DFS is observed after definitive treatment in SCC patients compared to adenocancer. OS is significantly reduced when RT is interrupted and in patients with three or more comorbidities.

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