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Original Article

Evaluation of Chemoradiotherapy Toxicity in Geriatric Patients Diagnosed with Locally Advanced Non-Small Cell Lung Cancer

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SUMMARY

Background: Geriatric patients diagnosed with locally advanced lung cancer often cannot access appropriate treatment options due to the increasing prevalence of comorbidities and poor performance status. Although, curative and palliative treatment options substantially contribute to survival of patients in the early and advanced stages of lung cancer. The present study aims to investigate treatment response and treatment complications in geriatric patients receiving chemotherapy with the diagnosis of locally advanced lung cancer.

Method: The study included outpatients admitted to our hospital between January 2016 and March 2021 who subsequently received chemoradiotherapy after being diagnosed with locally advanced non-small cell lung cancer. The patients were divided into two groups as patients aged 65 years and older and younger. The primary end-point of the study was the evaluation of treatment complications between the two groups. The secondary end-point of the study was the evaluation of treatment response, treatment interruption/discontinuation and hospitalization.

Results: The study comprised a total of 132 patients, including 67 patients aged ≥ 65 years. In the comparison of treatment complications between the two groups, the number of patients developing complications, the treatment interruption/discontinuation and the rate of hospitalization was significantly higher in patients aged ≥ 65 years ($p < 0.05$). The most common reason for hospitalization was pneumonia, which occurred significantly higher in patients aged ≥ 65 years ($p = 0.020$).

Conclusion: Although treatment responses are similar to elderly patients, treatment complications and hospitalizations are higher in elderly patients. Therefore, careful follow-up and symptom palliation are very important during the treatment process in these elderly patients.

1. Introduction

Lung cancer ranks first among cancer-related deaths worldwide.[1] The incidence of lung cancer in older patients increases in parallel to the aging of the world's population.[2] Geriatric patients generally cannot access appropriate drug options due to increasing comorbidities with increasing age, poor performance status, polydrug use, and the fact that geriatric patients are often excluded from the clinical trials.[3] Surgery can be overlooked as an option in older patients with early-stage and locally advanced lung cancer and these patients may not access curative treatment options. In fact, curative and palliative treatment options significantly contribute to the survival of patients with early-stage and locally advanced lung cancer.[4] Patients with locally advanced lung cancer represent a large group among patients with lung cancer in terms of the availability of curative treatment options. However, chemoradiotherapy (CRT) is recommended as the standard therapy in patients with inoperable tumor but good performance status (Eastern Cooperative Oncology Group [ECOG] PS 0–1).[5] It is known that curative therapies are less applicable in older patients with locally advanced lung cancer than in younger patients.[6] The studies, on the other hand, demonstrated significant contribution of CRT to survival in this patient group, particularly in those with good ECOG performance status.[7] The increasing rate of comorbidities with increasing age complicates treatment in this group of patients. There is an increased rate of mortality related to secondary cardiovascular complications in this group of patients.[8] Based on this data, the present study was designed to evaluate treatment complications and treatment responses in patients aged 65 years and older and patients younger than 65 years receiving CRT after being diagnosed with locally advanced non-small cell lung cancer.

2. Material and method

The study included outpatients admitted to the Palliative Care Outpatient Clinic at Ministry of Health Ankara Ataturk Chest Diseases and Thoracic Surgery Education and Research Hospital between January 1, 2016 and March 1, 2021 who subsequently received CRT after being diagnosed with locally advanced non-small cell lung cancer. The study included patients who have received CRT (concurrent/sequential) with a nodal stage of N2/N3 and patients with

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N0/N1 disease who were deemed medically inoperable. Patients diagnosed with small cell lung cancer, patients who have received neoadjuvant/adjuvant CRT before/after surgery, patients with a performance status of 3–4 who are ineligible to CRT and those receiving immunotherapy were excluded. The patient data in the archived records and automation system was retrospectively reviewed. The patients included in the study underwent re-staging according to the 8th edition of the TNM classification system. Demographic data of the patients (i.e. age, gender), comorbidities (i.e. chronic obstructive pulmonary disease [COPD], diabetes mellitus, hypertension), ECOG performance status (at the beginning/at the end of therapy), pathological diagnoses (squamous/non-squamous) TNM stages, mode of therapy (sequential/concurrent), treatment complications, receipt of primary prophylaxis during therapy, number of hospital admissions, reasons for hospitalization, therapy completion status (postponement/discontinuation) and treatment responses were recorded. The patients were divided into two groups as patients aged 65 years and older (geriatric) and patients younger than 65 years. The treatment responses were evaluated as control computed tomography scans of the thorax at 3 and 6 months after the completion of therapy, and the treatment response was categorized in four groups according to the Response Evaluation Criteria in Solid Tumors (RECIST) as partial response, complete response, stable disease and progressive disease. The patients underwent control examination for the development of radiation pneumonia (RP) within 4–6 weeks with clinical examination and imaging studies. Patients found to have RP were recorded on the system.

A consultation with a neurologist was performed for patients reporting symptoms of neuropathy and patients diagnosed with neuropathy secondary to therapy by the neurologist were recorded on the system. A consultation with an internal medicine specialist was performed for patients reporting symptoms of esophagitis secondary to radiotherapy that started after therapy and patients diagnosed with esophagitis secondary to therapy were recorded on the system. The reasons for hospitalization (COPD exacerbation, supportive therapy, grade 3–4 neutropenia, grade 2 esophagitis) were recorded. Any failure in continuing therapy due to complications of radiotherapy or chemotherapy was recorded as interruption/discontinuation. The primary end-point of the study was defined as the comparison of treatment complications between the two groups. The secondary end-point of the study was the evaluation of treatment response, treatment interruption/discontinuation, hospitalization and its reasons. Ethics committee aproval was obtained for the study from the ethics committee of Ankara Atatürk Sanatorium Education and Research Hospital with the date of 15.04.2021 and the decision number 724.

2.1. Statistical analysis

The demographic characteristics of the study group were analyzed by using descriptive statistics (frequencies, proportions, and means (±SD or medians). Initially patients were divided into 2 groups according to age of 65 and compared in terms of treatment type, existance of comorbidities/COPD by using non-parametric test chi-square. Afterwards patients were re-grouped according to need of hospitalization, treatment complications and therapy completion status to determine related factors. So comorbidities, histopathological subtypes (squamous cell carcinoma [SCC]/adenocarcinoma [AC]), chemo-radiotherapy types (concurrent/sequential) and the presence of COPD were compared between 2 groups with chi-square test.

3. Results

The study comprised a total of 132 patients, including 67 patients aged ≥ 65 years old. The most common histopathological tumor type was squamous cell lung cancer in both groups (p = 0.61). The most common disease stage according to the TNM classification system was stage 3B (p = 0.31). The treatment given to the patients was often concurrent CRT in both groups (p = 0.22) (Table 1). In the analysis of comorbidities, there were 50 patients among those aged ≥ 65 years old and 41 patients among < 65 years old had at least one comorbid condition (p = 0.15), and COPD was significantly more common in the group of patients aged ≥ 65 years old (n = 42, p = 0.024). The analysis of factors that might have affected hospitalization in patients aged ≥ 65 years old revealed that the presence of comorbidities, histopathological subtypes (SCC/AC), CRT types (concurrent/sequential) and the presence of COPD had no significant effect on the hospitalization (p = 0.077, p = 0.79, p = 0.46, p = 0.06, p = 0.07, respectively) (Table 2). Similarly, the analysis of therapy completion status in patients aged 65 years and older revealed that the presence of comorbidities, histopathological subtypes (SCC/AC), CRT types (concurrent/sequential) and disease stage had not significant effect on completion of therapy (p = 0.77, p = 0.49, p = 0.09, p = 0.09, p = 0.41, respectively). A comparison of treatment complications between the two groups showed that the rate of complications was

Table 1
Demographic comparison of two groups.

Variables	Age ≥ 65 yr (n = 67)	Age < 65 yr (n = 65)	p value
Gender (K/E)	4/63	4/61	0.96
Smoking status			**0.005**
Former smoker	54	48	
Active smoker	0	9	
Unknown	13	8	
COPD	42	28	**0.024**
Comorbidity			0.15
Yes	50	41	
No	17	24	
Histopathology			0.61
Adenocarcinoma	18	15	
SCC	49	50	
Clinical T stage			0.78
T I-II	8	9	
T III	35	30	
T IV	24	26	
Clinical N stage (patolojik?)			0.25
N0	6	2	
N1	11	9	
N2	41	48	
N3	5	6	
TNM stage			0.31
IIIA	27	18	
IIIB	35	41	
IIIC	5	6	
Initial treatment			0.22
cCRT[1]	44	49	
sCRT[2]	23	16	
Radiotherapy technique			0.89
Convansionel RT	44	42	
IMRT[3]	23	23	
Primary prophylaxis[4]	19	16	0.62

[1] Concurrent chemoradiotherapy.
[2] Sequantial chemoradiotherapy.
[3] Intensity-modulated radiation therapy therapy.
[4] According to NCCN guideline for high risk patients granulocyte stimulant factor was administrated.

Table 2
Factors affecting hospitalization and treatment completition in the ≥ 65 years old group.

	Hospitalization (n = 28)	No hospitalization (n = 39)	p value	Treatment comleted (n = 62)	Treatment interrupted/ terminated (n = 5)	p value
Co-morbidity	24 (85.7%)	26 (66.6%)	0.077	46 (74.1%)	4 (80%)	0.774
Histopathology			0.790			0.491
SCC	20 (71.4%)	29 (74.4%)		46 (74.2%)	3 (60%)	
Adenocarcinoma	8 (28.6%)	10 (25.6%)		16 (25.8%)	2 (40%)	
CRT type			0.469			0.093
Concurrent CRT	17 (60.8%)	27 (69.2%)		39 (62.9%)	5 (100%)	
Sequential CRT	11 (39.2%)	12 (30.8%)		23 (37.1%)	0	
Radiotherapy			0.060			0.093
Convantional	22(78.6%)	22 (56.4%)		39 (62.9%)	5 (100%)	
IMRT	6 (21.4%)	17 (43.6%)		23 (37.1%)	0	
TNM stage			**0.005**			0.416
IIIA	5 (17.8%)	22 (56.5%)		26 (41.9%)	1 (20%)	
IIIB + IIIC	23 (82.2%)	17 (43.5%)		36 (58.1%)	4 (80%)	

significantly higher in patients aged ≥ 65 years old (n = 51) and the most common complications were radiation esophagitis, RP and peripheral neuropathy (p = 0.012). The rate of hospitalization was higher in patients aged ≥ 65 years old (1.31 versus 0.58). The most common reason for hospitalization was pneumonia, which occurred significantly more often in patients aged ≥ 65 years old (n = 16) (p = 0.02). The number of patients who have interrupted or discontinued therapy was significantly higher in the group of patients aged ≥ 65 years old (n = 28) (p = 0.036). The analysis of treatment response revealed that partial response was the most common in the two groups, without any significant difference between the groups (p = 0.44) (Table 3).

Table 3
Treatment complicationss, frequncy of completion of therapy and response rates.

Variables	Age ≥ 65 yr (n = 67)	Age < 65 yr (n = 65)	p value
Complication (n, %)			**0.012**
Radiation pneumonitis (Grade ≥ 2)	13 (19.4%)	5 (7.6%)	
Esophagitis (Grade ≥ 2)	17 (25.3%)	9 (13.8%)	
Thrombocytopenia	6 (9%)	2 (3.2%)	
Peripheral neuropathy	13 (19.4%)	6 (9.2%)	
Total complication	49 (73.1%)	22 (33.8%)	
Reason for hospitalization			**0.020**
Esophagitis	7 (10.4%)	7 (10.7%)	
Hematological toxicity	1 (1.4%)	1 (1.5%)	
Pneumonia	16 (23.8%)	4 (6.1%)	
Total hospitalization	24 (35.6%)	12 (18.3%)	
Disruption/discontinued of treatment	28	16	**0.036**
Response status			0.445
Partial response	52	55	
Stable disease	14	10	
Progression	1	-	
Hospitalization rate	1.31	0.58	

4. Discussion

Patients with locally advanced lung cancer account for 30–35% of patients diagnosed with non-small cell lung cancer. Locally advanced lung cancer consists of a group of patients that can be staged in a wide spectrum according to the 8th edition of the TNM classification system for whom a wide variety of treatment methods can be used with the addition of targeted therapies in lung cancer. However, CRT still remains the mainstay of treatment in this group of patients.[9,10] Appropriate treatment methods can sometimes be delayed or never administered to those patients who are diagnosed with locally advanced lung cancer in older ages due to such concerns as complication risks, performance status and presence of comorbidities. Some studies have demonstrated that advanced age, poor performance status and T and N stages negatively affect survival in this patient group.[11] Another study conducted on patients aged 70 years and older with locally advanced lung cancer has demonstrated survival advantage of concurrent and sequential CRT over chemotherapy and radiotherapy alone. Poor performance status has been identified as a factor negatively affecting survival.[7] Another study found that CRT provided survival advantage in older patients with locally advanced lung cancer, and ECOG performance status and disease stage were identified as factors negatively affecting survival.[12] The present study included patients with an ECOG performance status of 0–1 and upon completion of therapy with this performance status at this age, cell type, type of treatment, presence of comorbidities and disease stage had no effect on survival; there was also no significant difference between the two groups in terms of treatment response, the most common type being partial response in both groups. The treatment response of geriatric patients can be found to be similar to that of young patients and survival benefit can be achieved, provided that the patients have good performance status and CRT is administered in a timely manner.

CRT can be administered concurrently or sequentially. Concurrent administration of chemo- and radiotherapy provides significant survival advantage and chance of local control, although this mode of administration is associated with an increased risk of esophagitis.[13] In the present study, concurrent CRT was more commonly used in both groups and although hospital admission due to treatment complication was more common in patients over 65 years old, there was no difference in terms of treatment response.

An association between COPD and lung cancer is commonly observed due to smoking being a common risk factor. This association is often encountered in older people with aging and prolonged duration of smoking.[14] Poor performance status arising from COPD exacerbations or the association of these two conditions may preclude treatment or cause an interruption in the treatment of these patients. The control of respiratory symptoms and effective use of bronchodilator therapy is particularly important in the treatment of this patient group. The most common comorbidity encountered in the present study patients was COPD (p < 0.005). However, the presence of COPD neither caused a delay in the treatment nor affected hospitalization (p > 0.005).

CRT used in the treatment of locally advanced lung cancer can have various complications. Esophagitis, one of the complications of CRT, occurs within 2–4 week after therapy, impairing both patients'

life quality and possible interrupting the treatment process. High dose of RT is a risk factor for developing esophagitis. Some studies in literature report decreased incidence of esophagitis with age, while some others support the contrary.[15,16] In the present study, esophagitis was significantly more common in older patients. RP, another complication of CRT, occurs particularly within six weeks after the completion of RT; it can be progressive and as severe as to be life-threatening. Tumor size and location, high RT dose, extensiveness of RT site, smoking and age can be counted as risk factors for developing RP. Consistent with literature, RP was significantly more common in older patients in the present study.[17] Neuropathy secondary to the administration of platinum-based chemotherapy regimens that impairs patients' life quality and causes depression and immobilization occurs particularly after having received 1–2 cycles of CRT.[18] In the present study, the rate of neuropathy was significantly higher in older patients. Attentive follow-up and symptom palliation during and after therapy is therefore crucial to control treatment complications in geriatric patients.

Cytotoxic therapy in lung cancer patients can predispose to developing bacterial pneumonia by suppressing immunity. Pneumonia in this patient group can have a severe course, result in frequent emergency admissions and hospitalizations. Pneumonia increases mortality rate in this patient group.[19] Complications related to CRT and infections such as pneumonia can cause delays in the treatment or discontinuation of therapy by decreasing performance status and tolerance to CT in this group of patients who are otherwise eligible to curative intent treatment options. In the present study, both pneumonia was more common and therapy interruption or discontinuation was significantly more common in geriatric patient group. Attentive follow-up of geriatric patients from this perspective and the administration of appropriate treatment options is of vital importance to control complications, which have the potential of increasing mortality.

5. Conclusion

Treatment responses of geriatric patients with good performance status and locally advanced lung cancer undergoing CRT are similar to younger patients. Since peripheral neuropathy, radiation esophagitis and RP are common complications in the elderly patient group, it is important to follow up and treat these complications during treatment. Even though treatment complications are more common in this group of patients, continuation of therapy with careful follow-up and symptom palliation is important for disease control.

Conflict of interest

On behalf of all authors there is no conflict of interest or any financial support for this study.

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