Clinical and Laboratory Results and Prognosis Patients with Scleroderma: A Single Center Experience

Sklerodermalı Hastalarımızın Klinik ve Laboratuvar Sonuçları ve Prognozu: Tek Merkez Deneyimi

[1]Ebru Ozden Yilmaz, [2]Dondu Uskudar Cansu, [2]Cengiz Korkmaz

[1]Department of Internal Medicine, Eskişehir Osmangazi University, Eskisehir, Turkey
[2]Division of Rheumatology, Department of Internal Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

Abstract: Systemic scleroderma (SSc) is a rare connective tissue disease accompanied by progressive fibrosis. Especially pulmonary, cardiac and renal involvement is a major cause of morbidity and mortality in the disease while skin involvement and Raynaud's phenomenon (RP) can also decrease the quality of life by increasing morbidity. In this study, our aim was to determine the demographics, organ involvement and prognosis of our SSc patients followed up in Rheumatology department and compare the data with the literature. For this purpose, the data of 79 patients who were followed up in our department were evaluated retrospectively. 74 (93.7%) of the 79 patients were female, the mean age of the patients was 54.3 ± 12.7 (22-76) years and the mean duration of disease was 7.29 ± 7.02 years. 71 (89.8%) had limited cutaneous SSc (lcSSc), 6 (7.6%) had diffuse cutaneous SSc (dcSSc) and 2 (2.5%) had sine scleroderma. When the cumulative organ involvement of the patients was evaluated, it was seen that 73 (92.4%) had RP, 63 (79.7%) sclerodactyly, 14 (17.7%) digital ulcer and 22 (27.8%) telangiectasia. Eight (10.1%) patients had articular complaints. Antinuclear antibody (ANA) was (+) in 49 (62%) of the patients and anti-Scl-70 was (+) in 31 (39.2%). 74 patients (93.7%) were still alive and 5 (6.3%) died. No disease-related factor was found to be effective on mortality (p> 0.05). Malignancy was developed in 4 (5.1%) patients. Only high resolution computed chest tomography (HRCT) shot count were found to be an effective factor for cancer development (OR 1.74, p = 0.023 (CI 1.081-2.829). In conclusion, causes of mortality and malignancy were similar with the literature in patients we followed up with SSc. We found a correlation between the incidence of chest CT and the malignancy development unlike the literature. This result should be supported by studies involving larger patient numbers.

Key Words: scleroderma, prognosis, malignancy, mortality

Ozden Yılmaz E, Uskudar Cansu D, Korkmaz C. 2018, Clinical and Laboratory Results and Prognosis Patients with Scleroderma: A Single Center Experience, *Osmangazi Journal of Medicine*, 40(3):70-78 **Doi:** 10.20515/otd.415387

Özet: Sistemik skleroderma (SSk) progresif fibrozisle giden nadir görüln bir bağ dokusu hastalığıdır. Hastalıkta özellikle akciğer, kalp ve böbrek tutulumu önemli morbidite ve mortalite nedeni iken cilt tutulumu, Raynaud fenomeni (RF) gibi tutulumlar da morbiditeyi arttırarak yaşam kalitesini arttırabilmektedir. Bu çalışma ile amacımız, Romatoloji bölümünde takip edilen SSk'lı hastalarımızn demografik özellikleri yanında organ tutulumları ve prognozlarını belirleyerek literatür verileri ile kıyaslamaktı. Bunun için bölümümüzde takip edilen 79 hastanın verileri retrospektif olarak değerlendirildi. 79 hastanın 74 (%93.7)'ü kadın, hastaların yaş ortalaması 54.3 ± 12.7 (22-76) yıl, hastalık süreleri ise ortalama 7.29±7.02 yıl idi. 71 (%89.8)'inde sınırlı kutanöz SSk (skSSk), 6 (%7.6)'sında diffüz kutanöz SSk (dkSSk) ve 2 (%2.5)'sinde ise sine-skleroderma mevcuttu. Hastaların kümülatif organ tutulumu değerlendirildiğinde 73 (%92.4)'ünde RF, 63 (%79.7)'sinde sklerodaktili, 14 (%17.7)'sinde dijital ülser ve 22 (%27.8)'inde telenjiektazi mevcut idi. Hastaların 8 (%10.1)'inde eklem şikayeti mevcut idi. Hastaların 49 (%62)'unda antinükleer antikor (ANA) (+), 31 (%39.2)'inde anti-Scl-70 (+) idi. 74 hasta (%93.7) halen yaşamakta olup 5 (%6.3)'i ölmüştü. Mortalite üzerine etkili olabilecek hastalıkla ilişkili bir faktör saptanmadı (p>0.05). Hastaların 4 (%5.1)'ünde malignite geliştiği görüldü. Kanser gelişimi üzerine etkili olabilecek faktör olarak sadece yüksek rezolusyonlu bilgisayarlı akciğer tomografisi (HCRT) çekim sayısı saptandı (OR 1.74, p=0.023 (CI 1.081-2.829). Sonuç olarak SSk ile takip ettiğimiz hastalarda mortalite ve malignite nedenleri literatüre benzer şekilde iken literatürden farklı olarak sadece akciğer tomografi çekim sıklığı ile malignite gelişimi arasında ilişki saptadık. Bu sonucun daha büyük hasta sayılarını içeren çalışmalarla desteklenmesi gerekmektedir.

Anahtar Kelimeler: skleroderma, prognoz, malignite, mortalite

Özden Yılmaz E, Üsküdar Cansu D, Korkmaz C. 2018, Sklerodermali Hastalarimizin Klinik ve Laboratuvar Sonuçları ve Prognozu: Tek Merkez Deneyimi, *Osmangazi Tıp Dergisi,* 40(3):70-78 **Doi:** 10.20515/otd.415387

Geliş Tarihi / Received
15.04.2018

Kabul Tarihi / Accepted:
11.06.2018

Yazışma Adresi / Correspondence Address
Döndü ÜSKÜDAR CANSU
mail: ducansu@hotmail.com

1. Introduction

Systemic scleroderma (SSc) is a systemic rare connective tissue disease characterized by progressive thickening of the skin and plays a role in vasculopathy, immune activation and fibrosis in its development. Although it is seen more frequently in women (female / male: 7/1), the disease may develop at any age (1,2). SSc can cause clinical manifestations that can be seen with many different organ involvements. Skin involvement is the characteristic feature of the disease. Raynaud's phenomenon (RP) accompanies clinical presentation in almost all patients. Cardiac, pulmonary, gastrointestinal, and renal involvement can be seen with the disease. Demographic characteristics and organ/system involvement of the patients determine the prognosis of SSc. In general, the prognosis is worse in patients with clinical and serological features of diffuse cutaneous SSc (dcSSc). It was also found that the presence of male sex, disease starting after 40 years old, pre-existing hypertension and black race pointed to poor prognosis (3). The mortality rate of patients with SSc is higher than the general population. Pulmonary fibrosis, cardiac causes, pulmonary arterial hypertension and renal crisis are the most common causes of mortality in patients with SSc. Infections and malignancies are other important causes of mortality apart from organ involvement (4). It has been reported that the incidence of malignancy increases in SSc when compared to the general population. In a multi centered study, a relationship was found between bladder cancer and cyclophosphamide which is used as an immunosuppressive agent in SSc (5).

The primarily aim of our study is to determine the clinical and laboratory characteristics of our patients with SSc and factors affecting the prognosis, and secondly to determine the patients in which malignancy has developed and the malignancy related factors and to compare the results with the literature data to determine the differences.

2. Materials and Methods

Patient selection

Seventy-nine patients diagnosed with SSc according to the American College of Rheumatology (ACR) / The European League Against Rheumatism (EULAR) 2013 diagnostic criteria were evaluated retrospectively. Demographic characteristics, organ and system involvement, laboratory parameters, echocardiographic findings and lung tomography findings related to lung involvement were recorded from the patient's files and digital records during diagnosis and follow-up. Mean duration of follow-up, duration of illness, given treatments, SSc subgroup, RP presence as the first finding of disease, swallowing difficulty, pulmonary involvement, gastrointestinal tract involvement, renal involvement, articular involvement, skin involvement, skin findings at any time (cumulative) such as presence of RP, sclerodactyly, edema, digital ulcer, dermal atrophy, telangiectasia and calcification were recorded. The presence of pulmonary involvement, whether the involvement was detected on follow-up and symptoms, chest tomography findings, initial and maintenance treatment for lung involvement, treatment response status, and other treatments for resistant patients were identified. Laboratory parameters including detailed blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), anti-Scl-70 and anti-centromere antibody results, echocardiographic findings, pulmonary artery pressure (PAP) values and whether the right heart catheterization was performed, presence of pulmonary arterial hypertension (PAH), and cumulative treatments given to patients during the disease were recorded. Presence of malignancy developed during follow-up, type and outcome of malignancy if present, presence of mortality, mortality cause and time were also evaluated.

Patients diagnosed under 18 years old, patients with only one visit and without follow-up were excluded. The study was approved by the ethics committee of Eskisehir Osmangazi University Medical Faculty with

the decision dated 28.11.2016 and numbered 80558721 / G-328.

Statistical analysis

In the analysis of the variables taken into the study, continuous data were given as the mean ± standard deviation (SD), and categorical data were given as frequency and percentage. For the statistical evaluation of the findings, IBM SPSS for Windows version 21.0 was used. In the analysis of categorical data (cross-tables) Pearson chi-square, Pearson exact Chi-square and Yate's Chi-square analysis were used. A stepwise method was used in the binary logistic regression analysis to determine which of the independent markers (variables) that were considered to affect the malignancy were at the major level.

3. Results

74 (93.7%) of 79 patients were female. The mean age of the patients during diagnosis was 54.3 ± 12.7 (22-76) years and mean duration of disease was 7.29 ± 7.02 years. 71 patients (89.8%) had limited cutaneous SSc (lcSSc), 6 (7.6%) had dcSSc and 2 (2.5%) patients had sine-scleroderma when clinically classified. As initial finding; RP was found in 72 (91.1%) of patients, skin involvement in 71 (89.9%), swallowing difficulty in 14 (17.7%) and lung involvement in 21 (26.6%). When the cumulative organ involvement of the patients was evaluated, 73 (92.4%) had RP, 63 (79.7%) sclerodactyly, 14 (17.7%) digital ulcers and 22 (27.8%) telangiectasia. 8 (10.1%) of the patients had joint involvement. Of the patients, 49 (62%) were ANA (+) and 31 (39.2%) were anti-Scl-70 (+). (Demographic characteristics, clinical findings, laboratory results and medical treatments of the patients during diagnosis and follow-up were given in Table 1).

Table 1.
Demographic characteristics, clinical findings and laboratory results of patients with scleroderma during diagnosis and follow-up period

N	79
Sex, n (Female/Male)	74/5
Age, mean±SD, (min-max), years	54.37±12.74 (22-76)
Age of diagnosis, mean±SD, (min-max), years	46.73±13.40 (12-73)
Follow up duration, mean±SD, (min-max), years	5.1±4.11 (0.25-18)
Duration of disease, mean±SD, (min-max), years	7.29±7.02
Initial finding	
Raynaud phenomenon, n, (%)	72 (91.1)
Dysphagia, n, (%)	14 (17.7)
Lung involvement, n, (%)	21 (26.6)
Skin involvement, n, (%)	71 (89.9)
Type of Systemic Scleroderma	
Diffuse, n, (%)	6 (7.6)
Limited, n, (%)	71 (89.8)
Sinescleroderma, n, (%)	2 (2.5)
ANA positivity, n, (%)	49 (62.8)
Anti-Scl-70 positivity, n, (%)	31 (39.7)
Sclerodactyly, n, (%)	63 (79.7)
Presence of digital ulcer, n, (%)	14 (17.7)
Telengiectasia, n, (%)	22 (27.8)
Prolonged esophagus motility, n, (%)	37 (46.8)
Frequency of lung involvement, n, (%)	47 (59,5)
Presence of pulmonary arteriel hypertension, n, (%)	4 (5)
Treatments	
Hydroxychloroquine, n, (%)	28 (35.4)
Corticosteroid, n, (%)	53 (67.1)
Azathioprine, n, (%)	33 (41.8)
Calcium channel blocker, n, (%)	61 (77.2)
Nifedipine, n, (%)	57 (72.2)
Amlodipine, n, (%)	4 (5.1)
Acetylsalicylic acid, n, (%)	60 (75.9)
Proton pump inhibitor, n, (%)	64 (81)
Metoclopramide, n, (%)	27 (34,2)
Cyclophosphamide IV, n, (%)	32 (40,5)
Cyclophosphamide PO, n, (%)	17 (21,5)

Pulmonary involvement was present in 47 (59.5%) of the patients. Of the 47 patients, 43 had interstitial lung disease (ILD) and 4 had ILD + pulmonary arterial hiypertension (PAH). 38 (80.9%) of the 47 patients with ILD had pulmonary involvement at the time of diagnosis and 9 (19.1%) of them had shown pulmonary involvement at follow–up period. Twelve out of the 44 patients with ILD who had immunosuppressive therapy were still on first-line treatment and had not yet undergone maintenance treatment. Symptoms of patients with pulmonary involvement, initial HRCT findings, given treatments and treatment responses are presented in Table 2. When the patients with and without pulmonary involvement were compared, there was no statistically significant difference in terms of gender, initial findings, RP, swallowing difficulty, skin involvement ($p> 0.05$). When the relationship between the clinical findings and pulmonary involvement of the patients was examined, a significant relationship was detected only between the presence of telangiectasia and pulmonary involvement ($p=0.037$). Telangiectasia was less common in those with pulmonary involvement. There was no significant relationship between other findings and lung involvement ($p>0.05$).

Table 2.
Symptoms and treatments of patients with scleroderma and pulmonary involvement

Feature	N (%)	Total n (%)
Detection time of lung involvement		
At the diagnosis	38 (80.9)	47 (100)
During follow up	9 (19.1)	
Symptom		
Asymptomatic	27 (57.4)	
Effort dyspnea	18 (38.3)	47 (100)
Cough	2 (4.3)	
First treatment agents		
Cyclophosphamide (intravenosus) + steroid	30 (68.2)	
Cyclophosphamide (oral) + steroid	11 (25)	44 (100)
Azathioprine + steroid	3 (6.8)	
Maintenance therapy		
Azathioprine	30 (93.8)	32 (100)
Methotrexate	2 (6.3)	
The first HRCT finding of lung involvement		
Fibrosis	8 (17)	
Ground-glass opacity	38 (80.9)	47 (100)
Peribronchial thickening	1 (2.1)	
Number of patients responding to treatment after the first 6 months	26 (84.2)	32 (100)
Treatment given to unresponsive (resistant) patients after the first 6 months		
Cyclophosphamide	3 (50)	
Rituximab	2 (33.3)	6 (100)
Mycophenolate mofetil	1 (16.7)	

In 34 (43%) of 79 patients pulmonary artery pressure (PAP) was presented in the echocardiography performed. The PAP level of these patients was 30.6 ± 8.9 mmHg (15-60). Right heart catheterization was performed on 9 patients who were found to have PAP> 40 mmHg on echocardiography. Four patients (5.1%) were diagnosed PAH with right heart catheterization. In 2 (50%) of this group PAH was detected at the diagnosis of scleroderma and in 2 (50%) during follow-up. All of the 4 patients also had ILD at the same time. Of 4 patients with PAH, 2 (50%) were given bosentan, 1 (25%) ambrisentan + tadalafil and

1 (25%) ambrisentan + bosentan + epoprostenol. One (1.3%) of the patients had pericardial effusion.

In the final analysis of the patients, 74 patients (93.7%) were still alive and 5 (6.3%) patients died. The mean age at the time of mortality was 66.6 ± 5.7 years (57-72), whereas patients died at 15.7 ± 13.3th years (4-35) of the disease. When the causes of mortality in 5 deaths were examined, one patient had sepsis, 1 patient had metastatic lung cancer, 1 patient had infection due to febrile neutropenia after acute myeloid leukemia, 1 patient had respiratory failure due to pulmonary fibrosis and the other patient had gastrointestinal bleeding due to angiodysplasia. (The detailed characteristics of the patients who developed mortality were given in Table 3).

Table 3.
Characteristics of patients with scleroderma developing mortality

Cases	**1**	**2**	**3**	**4**	**5**
Gender	Female	Female	Female	Female	Female
Duration of disease, years	8	20	13	4	35
Mortality age, years	57	66	69	69	72
Cause of mortality	Sepsis	Lung cancer	Acute myeloid leukemia	Lung fibrosis	GIT bleeding (angiodysplasia)

No disease-related factor was found to be effective on mortality (p> 0.05). There was no statistically significant difference in terms of pulmonary involvement, cardiac involvement, cyclophosphamide and azathioprine use, antibody positivity when comparing patients with and without mortality (respectively, p=0.07, p=1, p=1, p=1 and p=0.381).

Malignancy was developed in 4 (5.1%) of the patients during follow-up. Acute myeloid leukemia was observed in one patient, large-cell neuroendocrine lung cancer in one patient, small-cell lung cancer in one patient and papillary thyroid cancer in one patient (The characteristics of the patients with scleroderma in which malignancy was developed were given in Table 4)

Table 4.
Characteristics of the patients with scleroderma in which malignancy was developed

Cases	**1**	**2**	**3**	**4**
Age at diagnosis of scleroderma	56	50	46	45
Gender	Female	Female	Female	Female
The duration of SSc disease when cancer was detected	13	20	15	9
Type of cancer	Acute myeloid leukemia	Lung cancer	Lung cancer	Papillary thyroid cancer
Outcome	Ex	Ex	Alive	Ex

According to the logistic regression analysis, in which the factors related to the disease that may affect the development of cancer, the agents including cyclophosphamide and azathioprine use, and the number of HRCT shots (the mean number of HRCT shots in the cohort was 3.8 ± 2.4 (1-10 times) were also evaluated, it was determined that the total number of HRCT shots increased the cancer development 1.7 times (OR 1.74, p = 0.023

(CI 1.081-2.829). There was no correlation between the use of cyclophosphamide or azathioprine and the development of cancer (respectively, p=0.097 and p=0.995).

4. Discussion

SSc is a rare connective tissue disease. Most of our patients were female as expected in accordance with the work of Khanna et al. (6). In a study including 209 SSc patients conducted by Arandia et al., the age of diagnosis was 51.2 years, follow up period was 9.3 years and duration of disease was 16.1 years (7). In our study, the diagnosis age was earlier as 46.7 years, the follow-up period was shorter and the disease duration was shorter as 7.2 years.

Among laboratory tests, especially among autoantibodies, anti-Scl-70 and anti-centromere antibody is diagnostic for SSc beside ANA. In the study conducted by Talotta et al., in 74 (91.3%) of 81 SSc patients ANA was (+) and in 19 (23.4%) anti-Scl-70 was (+) (8). In studies conducted by Radic et al. 49 of 49 patients were found to have ANA (+) and 28 of the 49 patients had anti-Scl-70 (+) (9). 49 (62%) of our patients were found to have ANA (+) and 31 patients (39.2%) anti-Scl-70 (+) at the time of diagnosis. 1 of 31 patients with anti-Scl-70 (+) were included in the dcSSc subtype, 29 in the lcSSc group.

Skin involvement in SSc patients is the characteristic feature of the disease. Skin involvement can be seen as RP, sclerodactyly, digital ulcer, telengiectasis, edema and calcification. RP is the earliest finding of SSc, digital ulcer can be seen in %50 of patients (10,11). The study including 209 SSc patients conducted by Arandia et al. RP was found in 173 patients and skin involvement in 6 patients as initial finding. The cumulative clinical features of this study were RP in 202 patients, telengiectasia in 129 patients, digital ulcer in 89 patients and esophageal involvement in 26 patients (7). When we look at the initial findings of our cases, we found that RP is the most common finding and followed by skin involvement.

Pulmonary involvement in SSc can be seen in two groups as ILD and PAH. ILD is one of the main types of pulmonary involvement in SSc. ILD presents as exercise dyspnea and fatigue during the first 2-3 years of illness (12). The prevalence of PAH ranges from 10-15%. Risk factors for PAH are male sex, having more than 60 years of age, World Health Organization functional class IV pulmonary hypertension, countless telengiectasia, anti-centromere antibody positivity, and elevated serum uric acid levels (13-14). SSc patients with pulmonary involvement have worse prognosis (15). In a study conducted by Arakkal et al., 21 of 28 SSc patients were diagnosed with ILD and 6 with PAH. Of the 21 patients with ILD, 14 (66.7%) had dcSSc and 7 (33.3%) had lsSSc. A variety of cardiopulmonary symptoms were reported in 18 of 28 patients, including dyspnea (64.3%), cough (32%) and chest pain (10%). Ground glass densities were detected in 14 of 21 patients with ILD as HRCT findings (16). In a study comparing HRCT images of 162 SSC patients conducted by Goldin et al., ground glass density was detected in 49.4% and fibrosis was detected in 32.7% (17). In our study, 59.5% of 79 patients had pulmonary involvement. Of the 47 patients, 43 had ILD and 4 had ILD + PAH. Of the 47 patients with pulmonary involvement, 40 had lcSSc and 5 had dcSSc. Of the 47 patients with ILD, 27 were asymptomatic and 18 had exercise dyspnea. In the HRCT of cases, fibrosis was found in 8 cases and ground glass density was detected in 38 cases. The frequency of ILD was similar with the literature. However, no significant risk factor for ILD was found. In SSc patients with ILD, the first agent to be used in medical therapy is corticosteroids. The most important immunosuppressive agent that can be used as a corticosteroid dose reducing agent is cyclophosphamide. In a randomized study involving 45 patients with SSc + ILD, corticosteroid + intravenous cyclophosphamide was given for six months (18). In our study, 44 of 47 patients with pulmonary involvement were treated. The most commonly used agent as induction therapy was cyclophosphamide, similar with the literature. At the end of the sixth month, 84.2% of the 32 patients whose first-line treatment was completed had a response.

There is a significant increase in the risk of mortality in patients with SSc. Most deaths among SSc patients are associated with pulmonary fibrosis, PAH, or cardiac causes (4,19). Due to the complexity, diversity and multisystem involvement of disease symptoms in SSc patients it is difficult to connect deaths only to SSc. Causes of mortality due to SSc responsibility is responsible from 47.6% to 68% of deaths in SSc patients and usually related to organ involvement such as heart, pulmonary, renal and rarely gastrointestinal system (20). Non-SSc related causes of death include malignancy, infection and atherosclerotic, cerebrovascular or cardiovascular events (21). Various serologic, imaging and clinical features of SSc patients were found as independent predictors of mortality. It was observed that increased risk of mortality was associated with advanced age, male sex, emergency admission, duration of disease, low forced vital capacity, presence of PAH or ILD, diffuse and rapid skin involvement, coronary diseases, congestive heart failure, renal crisis and renal involvement. In a study involving 2691 SSc patients who were followed over a period of 40 years, the mortality rate was found to be 4 times higher than the general population. Cardiac involvement occurred in 2% of patients and was the leading cause of death. This was followed by pulmonary involvement, malignancy, and renal involvement (22). In the study including 188 patients conducted by Monaco et. al 5 patients died. When the causes of death were considered, 1 was due to sepsis, 3 had congestive heart failure associated with pulmonary involvement, and 1 was due to small-cell lung cancer (23). In our study, 5 (6.3%) out of 79 SSc patients died. All 5 patients were female and 3 had lcSSc while 2 had dcSSc. Similar to the literature, 2 (40%) patients died due to SSc-related causes and 3 (60%) to non-disease causes. When the factors affecting mortality were examined, mortality was found to be significantly associated with advanced age and heart failure, and there was no correlation between pulmonary involvement, malignancy and mortality, similar to the literature. All of the patients who died were women, contrary to literature. It was thought that this situtation was due to the fact that the number of dead patients was low and the majority of patients were women.

It has also been reported that the incidence of malignancy increases in SSc when compared with the general population. The most commonly seen malignancies are lung cancer and non-Hodgkin lymphoma. Other malignancies detected in SSc include skin cancer, thyroid cancer, hepatocellular carcinoma, oropharyngeal cancer and esophageal cancer (24). The risk factors predisposing to the development of malignancy in SSc patients are not clearly defined and the pathogenic basis of the relationship is not yet defined (25). In a large cohort study, malignancy detection rate was higher in males comparing to females (26). The immunosuppressive agents (especially cyclophosphamide) used in the treatment of SSc increase the risk of malignancy. The incidence of lung cancer observed in SSc patients was reported as high as 5% in the Italian cohort study. In the same study, the risk of developing lung cancer was significantly increased in young patients with SSc diagnosis, in patients with positive anti-Scl-70 antibodies, and in patients with pulmonary fibrosis (27). In our study, 4 (5%) patients developed malignancy during follow-up. All of the patients were women. We conclude that our results differ from the literature due to the low number of patients with malignancy, the high number of patients belonging to subscale lcSSc and the majority of patients being women. When the disease-related factors, gender, age of diagnosis, use of cyclophosphamide and azathioprine, and HRCT shot counts were evaluated, HRCT shots were found to increase cancer development, whereas no relationship was found between the use of cyclophosphamide or azathioprine and cancer development. In SSc patients, HRCT is recommended to detect pulmonary involvement or to monitor patients with involvement in every 6-12 months alongside with pulmonary function tests according to the guidelines. Large epidemiological studies are yet to be conducted in CT-related cancer risk researches. Gonzalez et al. emphasized that in 2007 a total of 72 million CT examinations

were associated with 29,000 radiation-related cancers (28). In our study, there was a significant relationship between the incidence of tomography and cancer development. However, since smoking is not questioned in the whole patient cohort, which may lead to malignancy, and the genetic makeup of the patients and the therapies they use may have been confounding factors, it is not possible to link cancer development to radiation alone.

In conclusion, in our SSc cohort, the demographic characteristics of the patients were similar with the literature and we could not find a variable that could affect the prognosis. However, our study is the first study to show the relation between the frequency of lung tomography shots and cancer development in SSc. The low number of cases in this study makes generalization difficult. According to the current guidelines, there is a need for multi-centered study to propose changes in the frequency of HRCT shots.

Acknowledgment: *We would like to thank Muzaffer Bilgin for his assistance in the statistical analysis of our work.*

❖ *The study was carried out in Eskisehir Osmangazi University Medical Faculty Department of Internal Medicine, Division of Rheumatology.*

KAYNAKLAR

1. Bhattacharyya S, Wei J, Varga J. Understanding fibrosis in systemic sclerosis: shifting paradigms, emerging opportunities. Nat Rev Rheumatol. 2012;8:42-54.
2. Liakouli V, Cipriani P, Marrelli A, Alvaro S, Ruscitti P, Giacomelli R. Angiogenic cytokines and growth factors in systemic sclerosis. Autoimmun Rev. 2011;10:590-4.
3. LeRoy EC. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15:202-6.
4. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010;69:1809-15
5. Kaşifoğlu T, Bilge ŞY, Yıldız F, Özen G, Pehlivan Y et al. Risk factors for malignancy in systemic sclerosis patients. Clin Rheum. 2016;35:1529-33.
6. Khanna D, Denton CP, Lin CJ, van Laar JM, Frech TM, Anderson ME et al. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). Ann Rheum Dis. 2018;77:212-220.
7. Arandia NI, Pilar C, Castillo M, Argüelles DC, Martínez LT, Hernández G et al. Influence of antibody profile in clinical features and prognosis in a cohort of Spanish patients with systemic sclerosis. Clin Exp Rheumatol. 2017;35:98-105.
8. Talotta R, Bongiovanni S, Letizia T, Rigamonti F, Ditto MC, Atzeni F et al. Measurement of Serum Klotho in Systemic Sclerosis. Send to Dis Markers. 2017;2017:9545930.
9. Radić M, Kaliterna DM, Fabijanić D, Radić J. Prevalence of systemic sclerosis in Split–Dalmatia county in Southern Croatia. Clin Rheum. 2010;29:419-21.
10. Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. Nat Rev Rheumatol. 2012;8:469-79.
11. Denton C, Korn J. Digital ulceration and critical digital ischemia in scleroderma. Scleroderma Care Res. 2003;1:12-6.
12. Walker U, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis. 2007;66:754-63.
13. Mukerjee D, St George D, Coleiro B, Knight C, Denton C, Davar J et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis. 2003;62:1088-93.
14. Steen V, Medsger TA. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. Arthritis Rheum. 2003;48:516-22.
15. Varga J, King Jr TE, Axford JS, Hollingsworth H. Overview of pulmonary complications of systemic sclerosis (scleroderma). Up to date.com Literature review current through: Oct 2017.
16. Arakkal G, Chintagunta SR, Chandika V, Damarla SV, Manchala S, Kumar BU. Cardio-pulmonary involvement in systemic sclerosis: A study at a tertiary care center. Indian J Dermatol Venereol Leprol.. 2017;83:677.
17. Goldin JG, Lynch DA, Strollo DC, Suh RD, Schraufnagel DE, Clements PJ et al. High-

resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. Chest. 2008;134:358-67.
18. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum.. 2006;54:3962-70.
19. Al-Dhaher FF, Pope JE, Ouimet JM. Determinants of morbidity and mortality of systemic sclerosis in Canada. Semin Arthritis Rheum. 2010;39:269-277.
20. Rubio-Rivas M, Royo C, Simeón CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum. 2014;44:208-219.
21. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. Ann Rheum Dis. 2007;66:940-4.
22. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology. 2011;51:1017-26.
23. Monaco AL, Bruschi M, La Corte R, Volpinari S, Trotta F. Epidemiology of systemic sclerosis in a district of northern Italy. Clin Exp Rheumatol. 2011;29:10.
24. Rosenthal AK, McLaughlin JK, Linet MS, Persson I. Scleroderma and malignancy: an epidemiological study. Ann Rheum Dis. 1993;52:531-3.
25. Zeineddine N, El Khoury L, Mosak J. Systemic sclerosis and malignancy: a review of current data. J Clin Med Res. 2016;8:625.
26. Olesen AB, Svaerke C, Farkas D, Sørensen HT. Systemic sclerosis and the risk of cancer: a nationwide population-based cohort study. Br J Dermatol. 2010;163:800-6.
27. Colaci M, Giuggioli D, Sebastiani M, Manfredi A, Vacchi C, Spagnolo P et al. Lung cancer in scleroderma: results from an Italian rheumatologic center and review of the literature. Autoimmun Rev. 2013;12:374-9.
28. de González AB, Mahesh M, Kim K-P, Bhargavan M, Lewis R, Mettler F et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. Arch Intern Med. 2009;169:2071-7.

©Copyright 2018 by Osmangazi Tıp Dergisi - Available online at tip.ogu.edu.tr ©Telif Hakkı 2018 ESOGÜ Tıp Fakültesi - Makale metnine dergipark.gov.tr/otd web sayfasından ulaşılabilir.