

CLINICAL MANAGEMENT OF LUNG CANCER PATIENTS WITH RESPIRATORY SYMPTOMS DURING EPIDEMIC OF COVID-19

Pınar Kabalak¹, Derya Kızılgöz¹, Suna Kavurgacı¹, and Ülkü Yılmaz¹

¹Atatürk Göğüs Hastalıkları Ve Göğüs Cerrahisi Eğitim Ve Araştırma Hastanesi

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Abstract

Objective: There are many clinical conditions that need to be followed and treated during pandemic like lung cancer. Carrying out health care for these patients who are immune-suppressive require extra care. **Method:** Among 108 lung cancer patients who has been hospitalized during pandemic, 18 of them with respiratory symptoms were evaluated. **Results:** Median age was 64 ± 9.4 with male predominance (male $n=16$, female $n=2$). Thirteen of them was non-small cell lung cancer (NSCLC) and 5 of them was small cell lung cancer (SCLC). Nine (50%) patients were receiving chemotherapy. The most common symptom was shortness of breath ($n=14$, 77.8%), followed by fever ($n=10$, 55.6%). Findings confirmed on computed thorax tomography (CTT) were as follows: Consolidation ($n=8$, 44.4%), ground glass opacities ($n=8$, 44.4%) and thoracic tumour/mediastinal-hilar lymphadenopathy ($n=3$, 16.7%). Hypoxia was seen in 11 patients (61.1%). Twelve patients had elevation of LDH (median= 302 ± 197) and lymphopenia (median= 1055 ± 648). There were 5 (27.7%) highly suspected cases for COVID-19. Any of their nasopharyngeal swap was positive. Two of these 5 patients received COVID-19 specific treatment even they have negative PCR results for 3 times. They responded well both clinical and radiological. For one case with SCLC receiving immunotherapy metil-prednisolone was initiated for radiation pneumonitis after excluding COVID-19. **Conclusion:** In line with the health policies of the countries and the adequacy of the health system, the necessity of a multidisciplinary approach in the management and treatment of complications in patients with lung cancer becomes even more important in this pandemic.

What is known?

1. During new coronavirus pandemic, among patients with a history of malignant tumours, lung cancer is the most common cancer, but patients with lung cancer have no higher incidence of malignant events.
2. Cytotoxic therapies should be continued under the required isolation, multidisciplinary approach is necessary for these patients
3. In a patient with respiratory symptoms, if the new coronary pneumonia is excluded, the initiation of required treatments for other infectious agents should not be delayed.
4. For follow up patients telemedicine is a good alternative.

What is new?

1. This study reflects the real experience of a thoracic oncology palliative care unit during pandemic.
2. It has been demonstrated that radiological or clinical findings differ in patients with lung cancer with pulmonary symptoms compared to the normal population.

INTRODUCTION

Due to outbreak of a novel severe acute respiratory syndrome (SARS) coronavirus 2019-nCoV (COVID-19), at the end of 2019, all efforts of health-care workers and a large part of health centres had to be allocated

to overcome this epidemic. As increase in the prevalence of COVID-19, the routine diagnosis and treatment procedures of most of chronic illnesses has been affected. To prevent virus transmission from other patients or healthcare providers, strict protections are required. Therefore, a vital guidance and its' updates prepared by *World Health Organization (WHO)* should be followed (2). As each country's own epidemiological and clinical data about COVID-19 accumulates, they can modify the patient approach and clinical practice with their own guides, as in our country, Turkey (1).

Oncology practice is a more difficult clinical situation due to the immunosuppression secondary to tumour and the treatments given. Epidemiological data from China revealed that, while total mortality is 2.3%, it is 5.6% among patients with malignant tumour (3). Among patients with cancer, lung cancer (5/18, 28%) is the most common type, but patients with lung cancer have no higher incidence of malignant events (20% and 62%, respectively, $p = 0.294$) (4). So an additional concern is needed depending on the capabilities of the health systems of countries.

Another difficulty is differential diagnosis of infection related complications in lung cancer patients, especially in the epidemic process. If a suspected or confirmed case of COVID-19 pneumonia is diagnosed in a lung cancer patient, transfer to specially prepared hospital department for isolation must be provided (5). Possibility of false-negative detection of nasopharyngeal swabs for new coronavirus nucleic acids should be concerned and in case of persistence clinical suspicion, secondary sampling should be done (6). While waiting test results of COVID-19, other causes related to infection or non-infection (radiation pneumonia, immune-checkpoint inhibitor-associated pneumonia, progression, pulmonary embolism, cardiac insufficiency etc.) must be examined not to lose time.

After a thoracic surgery for lung cancer, in case of existence of indication for adjuvant therapy, decision should be given case by case. If patient with pathological stage IB- IIA, is elderly and has poor physical condition, the follow-up treatment plan should be considered using a network platform with relevant physician (5). For patients with pathological stage IIB-III A time for adjuvant chemotherapy can be extended. In the presence of pathological N2, presence of epidermal growth factor receptor (EGFR) gene mutations may be evaluated as one of the adjuvant treatment options (7).

In advanced stage patients without targetable mutation, initiating or continuing of chemotherapy must be comprehensively evaluated. Being in process of consolidation chemotherapy or 2 and above line protocols, getting fragile to prior chemotherapies are clinical factors to extend the interval of chemotherapy by close communication with physician (5).

So these study aimed to reveal, how lung cancer patients with respiratory symptoms were managed during epidemic in a thoracic oncology unite.

METHOD

Study was conducted in thoracic oncology palliative care unite in Atatürk Chest Disease and Thoracic Surgery Training and Research Hospital. We have retrospectively analysed lung cancer patients who hospitalized due to respiratory symptoms from 2020, March 11, the date of first seen COVID-19 in Turkey. Among 108 hospitalized patients 18 of them were included. Respiratory symptoms were defined as; cough, sputum, shortness of breath, haemoptysis, fever and coexistence of these symptoms. If patients had other symptoms causing major indications for hospitalization along with respiratory symptoms they were excluded. Patients demographic data like age, gender, TNM stage, therapies before hospitalization, physical examination findings (transcutaneous oxygen saturation (hypoxia was defined [?]88%), bronchospasm, dyspnoea, tachypne), laboratory parameters (LDH with range of 0-247 IU/L, haemogram analyses, C reactive protein), radiological findings on chest X-ray and high resolution thorax tomography (HRTT) were recorded. In our clinic all patients with signs of respiratory tract infection are examined for acid-resistant bacillus (ARB), bacterial and fungal culture examination. When required, considering epidemiological history and clinical symptoms, nasopharyngeal swabs for new coronavirus nucleic acids were obtained according to local guide for new coronavirus (1). In our country, a Covid-19 suspect case completes the diagnosis and treatment process in the hospital. Patients with suspected contact or high risk for COVID-19 had transferred to specially prepared

department for centralized isolation and treatment in hospital. In case of continuing clinical suspicion, a second swab was taken. On the other hand, the necessary tests for differential diagnosis were continued and empirical antibacterial treatment was started in all cases.

Study was approved by our hospital ethical committee with number 673-14.05.2020 and necessary permission was obtained from the Turkish Ministry of Health with application number of 2020-05-08T00_20_42.

RESULTS

Eighteen patients with median age of 64+-9.4 were included. There was male predominance (male n=16, female n=2). Among cases 13 of them was non-small cell lung cancer (NSCLC) (including 8 squamous cell and 5 adenocarcinoma) and 5 of them was small cell lung cancer (SCLC). Distribution of TNM stages was; there were 10 patients with stage IV, 6 patients with stage III, and 2 patients with early stages. Number of patients receiving chemotherapy was 9 (50%). Among these only one patient was under adjuvant therapies. Other treatments were as follows; palliative cranial radiotherapy (RT) for 1 patient, best supportive care for 3 patients, chemo-radiotherapy for 2 patients, immunotherapy for 1 patient and 2 patients were in process of follow-up after completion of planned treatment (Table 1).

The most common symptom was shortness of breath (n=14, 77.8%), followed by fever (n=10, 55.6%). Five patients had cough along with other symptoms. But in 16 patients (88.9%), many respiratory symptoms, at least two, were present together. All patients had fatigue, while 3 patients had severe myalgia (Table 1).

According to the results of the radiological evaluation, 14 (77.8%) patients had pathology on chest X-ray (e.g. consolidation, pleural effusion, cavity or solid opacities). Findings confirmed on computed thorax tomography (CTT) were as follows: Consolidation (n=8, 44.4%), ground glass opacities (n=8, 44.4%) and thoracic tumour/mediastinal-hilar lymphadenopathy (n=3, 16.7%). Five patients (27.8%) had pleural effusion on CTT. The parenchymal findings of these 5 patients with pleural effusion were in the form of consolidation or secondary changes to the tumour. No pleural effusion was detected in patients having ground glass opacities on CTT (Table 1).

Hypoxia was seen in 11 patients (61.1%). In 12 patient's elevation of LDH (median=302+-197) and lymphopenia (median=1055+-648) was observed (Table 1).

There were 5 (27.7%) highly suspected cases for new coronavirus requiring nasopharyngeal swap. None of them was positive for COVID-19. Two of these 5 patients received COVID-19 specific treatment while differential diagnosis was ongoing (Table 2, case number 1 and 3). Considering radiological features of these patients, 4 of them had ground glass opacities on CTT. One patient had consolidation and tumour progression on CTT but due to fever that does not respond to broad-spectrum antibiotics he was required COVID-19 PCR test and resulted negative (Table 2, case number 5). Gram negative bacillus growth in the sputum was the most common microbiological features.

Among covid-19 suspected patients (n=5), 3 of them responded to broad-spectrum antibiotic therapy. In one case (Table 2, case number 2) with SCLC receiving immunotherapy following chemo-radiotherapy within the scope of international, multi-centre clinical trial, he was diagnosed with radiation pneumonitis after excluding COVID-19 with negative nasopharyngeal swab. He responded well to metil-prednisolone treatment (Figure 1). For 2 patients (Table 2, case number 1 and 3), although 3 PCR results were negative, they were hospitalized in the isolated service and significant clinical and radiological results were obtained with covid-specific treatment (Figure 2 and 3).

During epidemic we were tend to avoid unnecessary minimal invasive procedures like bronchoscopy or endobronchial ultrasound (EBUS). Only 1 patient required bronchoscopy to obtain intra-bronchial secretion clearance and his bronchial lavage culture was positive for

Escherichia coli.

DISCUSSION

Chronic diseases are difficult to manage due to the coronavirus pandemic affecting the whole world. Cancer patients constitute the most important part of this group (3). Lung cancer cases, which have been shown to increase frequency, are an important subgroup (4). Each country strives to plan according to the adequacy and possibilities of its own healthcare services for the management of patients receiving cancer treatment. The main issue to focus in this study is symptoms that are overlapping for both lung cancer and new coronavirus. The main symptoms for COVID-19 are fever, cough, fatigue, slight dyspnoea that cause confusion in patients with lung cancer (5). Because many other reasons secondary to tumour or cancer treatments (surgery, chemotherapy, radiotherapy, immunotherapy or targeted therapies) can cause these symptoms to appear. In this pandemic process, it is important to maintain follow-up and treatment process of lung cancer patients by minimizing the risk of covid-19 transmission.

When compared clinical characteristics of our study population to features of COVID-19 patients, it is noteworthy that both of them have the 6th decade and male gender predominance (8). According to some suggestions on diagnosis and treatment strategies of lung cancer patients during outbreak of new coronavirus from China, which started to fight first, for highly suspected or confirmed patient must be transferred to specially prepared isolated department of hospital (5). Five suspected patients of current study had admitted to our outpatient clinic of chemotherapy unite and the differential diagnosis process took place in the isolated service until the covid-19 was ruled out.

Each case should be handled separately, especially in terms of treatments (chemotherapy, targeted therapies, immune-checkpoint inhibitor, radiotherapy etc.) they receive at the time of admission, history of suspected contact, visit to another country are important issues (6). Totally, there were 11 (61.1%) patients (including concurrent chemo-radiotherapy) receiving chemotherapy.

Even ground glass opacities are widely accepted radiological presentation of new coronavirus pneumonia, it can be presented in different manifestations in lung cancer patients (9). There are small number of cases in literature. One of them is a case diagnosed lung adenocarcinoma with simultaneous diagnosis of new coronavirus with RT-PCR. Even she had no covid-19 specific symptoms she had contact with an infected physician. There were no typical CTT findings (showed diffuse, irregular, small, ground-glass opacities with partial consolidation in bilateral lungs) even at the beginning (when she had no symptoms) and after occurring symptoms. Finally, her complaints and radiological findings were dedicated to obstructive pneumonia caused by the tumour (10). Another reported case is a male with age of 73, who had been operated for NSCLC in 2016. Even he had no COVID-19 suspected symptoms, the patient was diagnosed with COVID-19 with positive PCR in the PET-CT taken during re-staging. Bilateral diffuse, peripheral predominant ground-glass opacities suggesting active inflammatory processes on 18F-FDG PET/CT was the suspecting condition for new coronavirus pneumonia (11). The most common radiological findings in our cases were consolidation (44%) and GGOs (44%), even in 5 cases with highly suspicious for covid-19 (Table 2).

There were 5 (27.8%) patients with pleural effusion. However, in none of patients, pleural fluid was considered to be related to COVID. Thus in highly suspected group (Table 2) there were no patients with pleural fluid. Although cancer patients are not included, according to a meta-analyse with 4121 patients, pleural effusion (5.3%) was reported as rarest CTT imaging features in new coronavirus pneumonia (12).

Although complete clinical manifestation is not clear yet; fever, lymphopenia, leukopenia, new pulmonary infiltrates on chest radiography, and no response to antibiotics treatment are the most reliable clues for COVID-19 diagnosis. The diagnosis of COVID-19 must be confirmed by the reverse transcription polymerase chain reaction (RT-PCR) (13). But we already know there is a discrepancy between PCR results and CTT findings. According to data from China, while positive rates of RT-PCR assay was 59% (601/1014), CTT imaging had 88% (888/1014) positivity in suspected patients with COVID-19. Because there were, 308 patients with negative PCR results but having COVID-19 suggesting radiology. So when evaluated together with clinical findings, CTT findings are quite reliable for diagnosis (14). Considering that RT-PCR is not the gold standard in diagnosis of new coronavirus, clinical and radiological suspicion seems to be sufficient to start treatment early, especially in patients with lung cancer. In our study population there were 2 patients

who had negative PCR results along with highly suspected clinical and radiological findings (Table 1, case number 1 and 3). Both of them responded well to COVID-19 specific therapies not requiring intensive care unit (ICU) support (Figure 2).

Another case presentation is a stage IV lung adenocarcinoma patient from Italy. While he was under nivolumab therapy within a multicentre clinical trial almost for 6 months, also having partial response. He had admitted with severe dyspnoea, hypoxia, lymphopenia, increased C-reactive protein, transaminases and lactate dehydrogenase. His chest X-ray revealed reticular-interstitial addensative findings and his nasal swab was positive for COVID-19. Due to the rapidly worsening clinical condition, the patient died without receiving any of COVID-19 specific treatment (15). Of course, it is not possible to predict the treatment approach and prognosis in the presence of COVID in cancer cases receiving immunotherapy nowadays. In this sense, we would like to contribute by detailing a case in our study. There was a male receiving immunotherapy following chemo-radiotherapy within the scope of international, multi-centre clinical trial (Table 2, case number 2). On his first admission to outpatient chemotherapy clinic he had severe dyspnoea with oxygen saturation 83% in the room air. His laboratory revealed increased LDH, C reactive protein and lymphopenia. There were bilateral heterogeneous opacities on chest X-ray and bilateral ground glass areas with right hemi thorax predominance on CTT. The patient was quickly taken to isolated service. His nasal swab was negative for new coronavirus for 3 times than transferred to general ward. He had been administrated immunotherapy only for one cycle so it was too early to expect immunotherapy related interstitial pneumonitis. But chemo-radiotherapy was completed almost 4-6 months ago and his radiological features were attempt to appear on radiotherapy side (right hemi thorax). So he had been diagnosed with radiation pneumonia and well-responded to metil-prednisolone therapy (Figure 1).

CONCLUSION

With this study, we aimed to emphasize that the diagnosis, treatment and management of complications in lung cancer patients require more care than the normal population in the pandemic process. In the face of a multifactorial clinical condition such as the type of treatment, dose, duration of cytotoxic therapy they are taking, and stage of the disease, as clinicians, we should carry out the differential diagnosis process quickly by minimizing the risk of transmission. We need to accumulation of knowledge for these patients whose immunity has already been suppressed and cytokine responses have differentiated.

FIGURE LEGENDS:

Figure 1: Radiological features of patient with SCLC (limited disease) receiving immunotherapy after chemoradiotherapy with COVID-19 negative nasopharyngeal swap, diagnosed with radiation pneumonitis. **1A:** X-ray findings before on his first admission. **1B:** X-ray findings 10 days after metilprednisolone therapy. **1C-1D:** Bilateral ground glass opacities with right side predominance on CTT during first admission.

Figure 2: Radiological features of patient with NSCLC (locally advanced) who completed chemo-radiotherapy. Although his nasopharyngeal swab was negative for 3 times, he responded well to COVID-specific treatment both clinically and radiologically. **2A-2C-2E:** Bilateral ground glass opacities + alveolar consolidations on CTT during first admission. **2B-2D-2F:** Resolutions of CTT findings after completion of COVID-19 therapy.

Figure 3. Radiological features of patient who underwent left pneumonectomy. Although his nasopharyngeal swab was negative for 3 times, he responded well to COVID-specific treatment both clinically and radiologically. **3A-3C-3E:** Patchy ground-glass opacities on right hemithorax on CTT during first admission. **3B-3D-3F :** Resolutions of CTT findings after completion of COVID-19 therapy.

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Variables

Age (mean±SD)

Gender (Male/female)

Histopathology SCLC² NSCLC³ Adenocarcinoma Squamous cell carcinoma

TNM Stage Stage I-II Stage III Stage IV

Therapy Chemotherapy Palliative radiotherapy Immunotherapy Best supportive care Chemo-radiotherapy Treatment complete

Symptom Fever Shortness of breath Sputum purulence Cough Myalgia

Pathology on X-ray

Hypoxia

Variables

Lymphopenia
 Elevated lactate dehydrogenase
Tomography findings Consolidation Ground glass opacities Thoracic mass/Lymphadenopathy Pleural effusion

Table 1. General characteristics of study population

Case number	Age/ gender	Histopathology/ TNM stage	Treatment	CTT findings	PCR result	COVID treat- ment	Major symp- toms	Lymphopenia/ elevated LDH	St CO sp ser (d
1.	63	Adenocarcinoma/ Stage II	Pneumonectomy	Bilateral ground glass opacities	Negative	Yes	Fever Cough Dyspnea	+ / +	14
2.	50	SCLC ¹ / Limited disease S	Immunotherapy	Bilateral ground glass opacities	Negative	Yes	Cough Dyspnea	+ / +	7
3.	71	SCC// Stage III	Chemo- radiotherapy	Bilateral ground glass opacities + alveolar consolidation	Negative	Yes	Dyspnea Myalgia	+ / +	10
4.	54	SCC/Stage IV	Chemotherapy	Consolidation	Negative	No	Dyspnea Fever	+ / +	3
5.	47	SCC/Stage III	Chemotherapy	Progression of malignancy	Negative	No	Fever Dyspnea	+ / -	0

Table 2. Features of COVID-19 suspicious patients

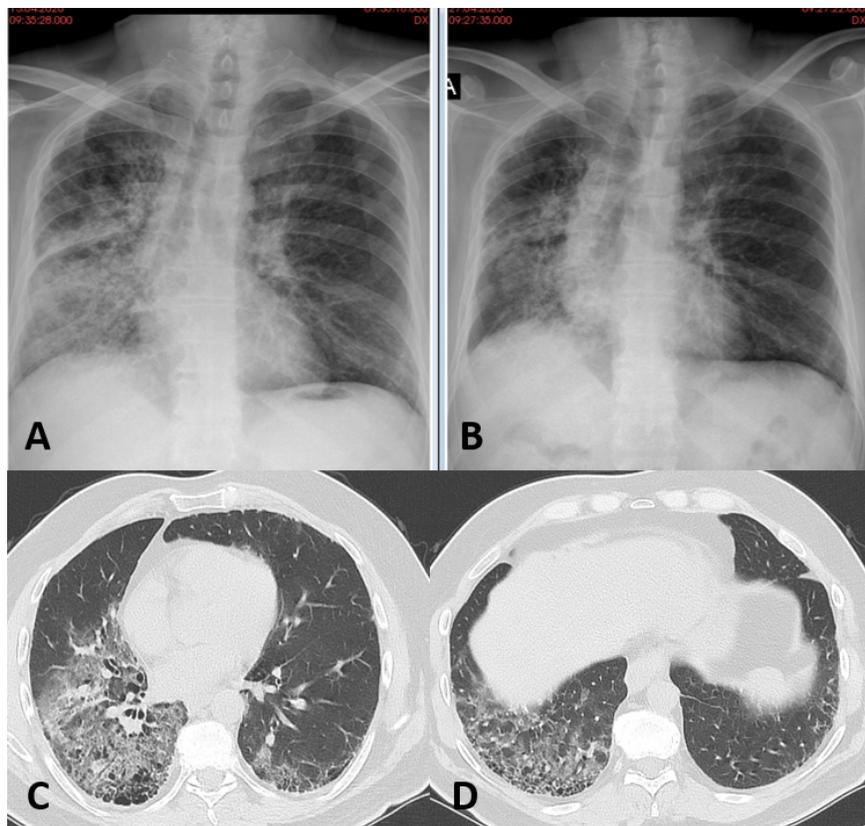
¹SCLC: Small cell lung cancer

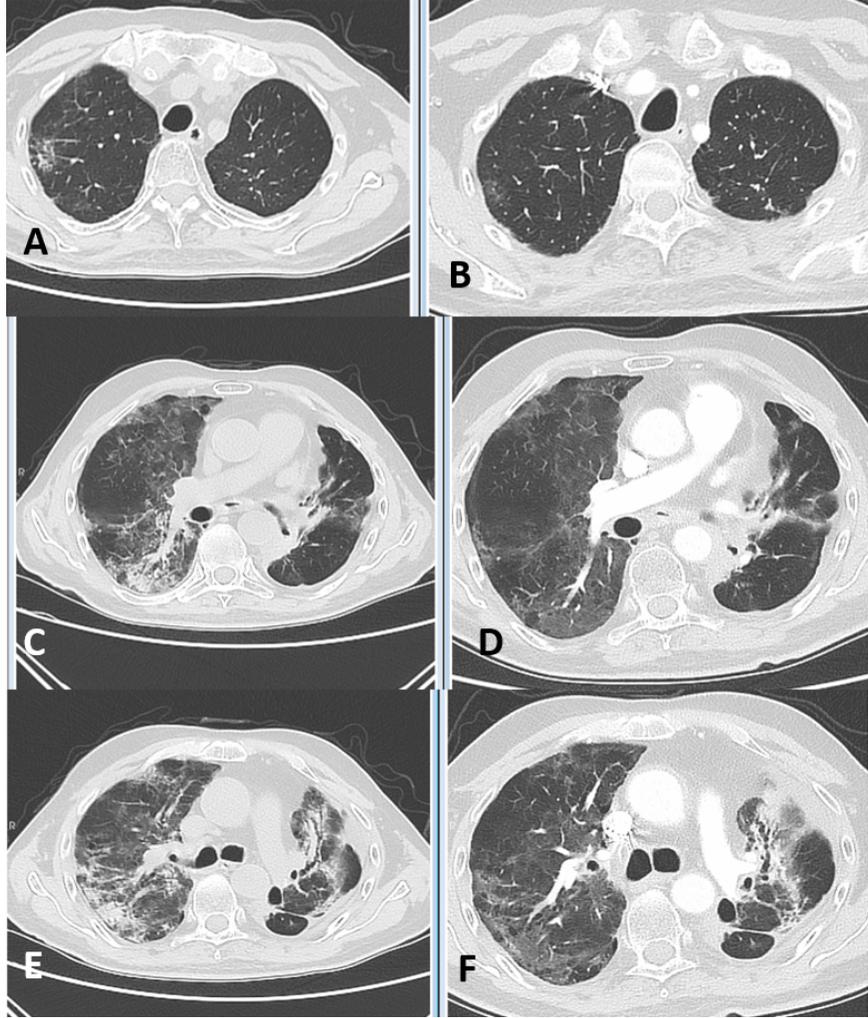
² Immunotherapy following chemo-radiotherapy within the scope of international, multi-center study

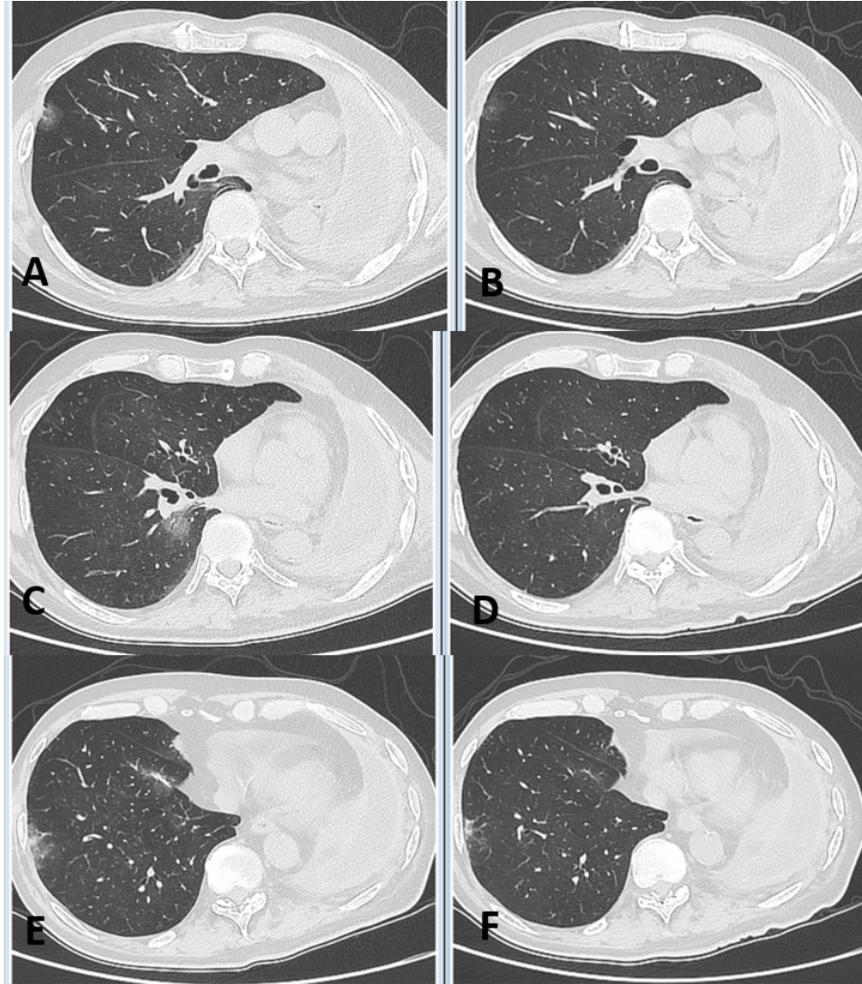
³ SCC: Squamous cell lung cancer

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