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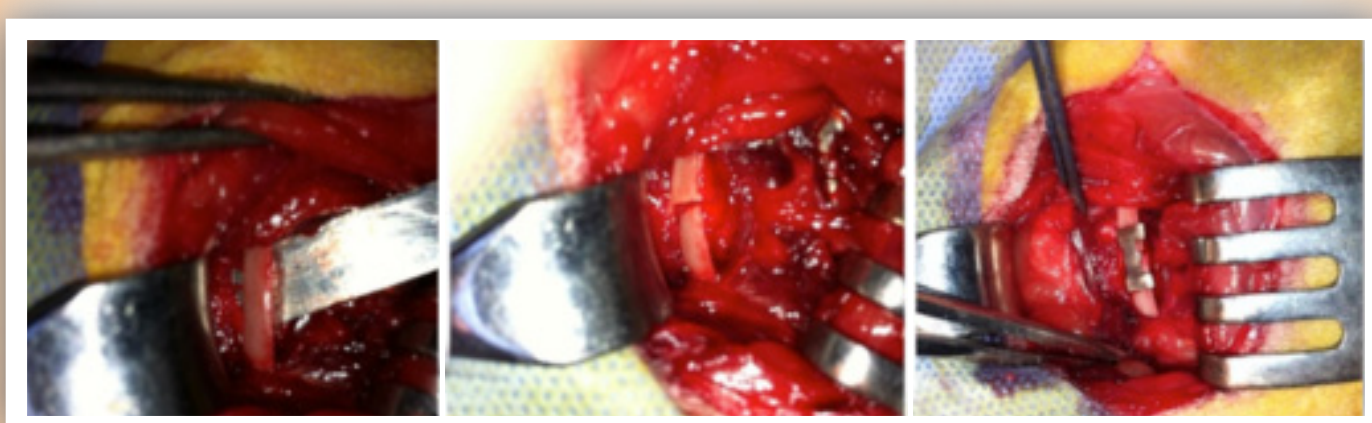

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The Current Thoracic Surgery is a current periodical, peer-reviewed and open access e-journal. It is the official e-journal of the Turkish Society of Thoracic Surgery and published three times annually.

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Original Article

Role of surgical fixation in rib fractures: an experimental study

Okan Karataş[1*], Hakan Işık[2], Kuthan Kavaklı[2], Ersin Sapmaz[2], Hasan Çaylak[2], Sedat Gürkök[2], Onur Genç[2], Alper Gözübüyük[2]

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ABSTRACT

Background: Rib fractures occur usually after thoracic traumas. Multiple and displaced fractures are occasionally associated with respiratory complications. That is why treatment for rib fractures should be done properly to prevent respiratory complications. This experimental study was performed to investigate the effects of early and late period rib fixation, on respiratory functions in an animal model with multiple displaced rib fractures, and to design a multiple displaced rib fracture treatment model.

Materials and Methods: Twenty-four, New Zealand rabbits were used in this study. The subjects are divided into three groups. All subjects' three consecutive ribs on right hemithorax were fractured and displaced surgically. Subjects in group I were observed without any further surgical process. In group II, subjects were undergone to a second surgery process to fix the fractured two ribs by titanium plate one week after the initial operation. In group III, subjects' three consecutive ribs were fractured and two ribs were fixed by titanium plates at the same operation session. Then subjects' respiratory functions, survivals and health status were observed.

Results: Oxygen saturation in first week ($p = 0.032$), clinical survival and health status were better than the other groups in group III. Fracture healing was better in fixation groups, radiologically and clinically.

Conclusions: Early rib fixation operation is recommended for multiple displaced rib fractures to prevent secondary respiratory complications.

Keywords: multiple displaced rib fracture, rib fixation, rib stabilization

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Introduction

Trauma is the major cause of deaths in the first four decades [1]. 20-25% of traumatic deaths are due to thoracic trauma and 25-50% of the remaining are accompanied by thoracic trauma [2,3]. About 60% of the patients with multitrauma have thoracic trauma, with 30-40% of them having rib fractures [4-6]. As it is so frequent, it should be treated appropriately.

The major goal in the treatment of patients with rib fractures is providing analgesia. If pain control is not optimized, complications such as atelectasis and infections are more frequently encountered [1-7]. It has been reported that, treatment options in patients with multiple rib fractures are associated with the number of fractures, location, age of the patient, and lung status [8-10]. Common indications for surgical treatment of rib fractures are flail chest, chest wall deformities / defects, pain, nonunion of fractures, symptomatic patients with three or more consecutive rib fractures [10-13].

On the other hand, surgical treatment of rib fractures is still controversial. There are numerous publications showing that early stage fixation (stabilization) is effective in preventing significant morbidities such as pain and infection in addition to a positive effect on lung function. Our clinical experience supports these findings, but there are no controlled animal experiments about this controversy. The aim of our study is to investigate effects of rib fixation surgery on respiratory functions in an experimental animal model.

Materials and Methods

Gulhane Military Medical Academy Animal Experiments Ethics Committee approved the study (12/2013-13/134). 24 New Zealand rabbits were used in the study. All subjects were adult females with an average weight of 3378 ± 405 gr. Subjects were subjected to humanitarian treatment in accordance with the Laboratory Animals Care and Use Guide. The number of subjects was determined by statistical preliminary study. The subjects were divided into 3 groups with equal numbers. There was no food or fluid restriction on subjects on preoperative period.

Surgery

After anesthesia and endotracheal intubation, the skin and subcutaneous layers were opened while the subject was in the right side up position followed by opening the periosteum of the ribs (Figure 1a). In group I (n=8) three consecutive ribs of the subjects were surgically fractured and displaced. The subjects were observed without rib fixation surgery (Figure 1b).

In group II (n=8) three consecutive ribs of the subjects were surgically fractured and displaced. After seven days as a late fixation model, subjects were performed rib fixation surgery on two displaced ribs with titanium plaques (Figure 1c). In group III (n=8) three consecutive ribs of the subjects were surgically fractured and displaced. As an early fixation model, subjects were performed rib fixation surgery on two displaced ribs with titanium plaques, concurrently.

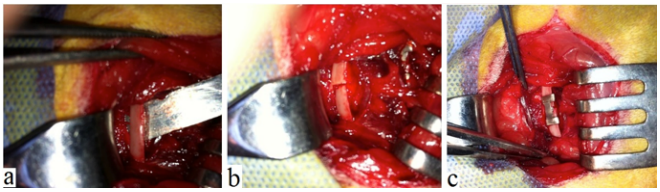

Figure 1a. Elevating the rib, **b.** Fractured rib, **c.** Fixed rib with titanium plate.

After surgery, medical treatment; antibiotherapy (Penicillin G 50.000 U/kg) and analgesic (Flunixinmeglumin 1.1 mg/kg) were ordered to the subjects for 3 days.

The subjects were taken into the cages alone at the postoperative period. All groups were followed in terms of their weight, heart and respiratory rate, chest x-ray, complete blood count (CBC) and, arterial blood gas sampling (ABG). During the follow-up period, attention was paid for adequate food and fluid intake, appropriate ambient temperature, being away from stressor factors (intense noise, light etc.) and giving appropriate medical treatment. Daily activity levels, food and water interest and, resting postures (pain posture) were observed. The effects of fixation on respiratory functions and healing process were evaluated in the obtained data. The animals were sacrificed on 3rd week under general anesthesia.

Statistical Analysis

The relationship between survival time, pre and postoperative weights, respiratory and pulse rates, saturation values, ABG and CBC parameters of the experimental groups were determined in the SPSS 15.0 package program; as well as the descriptive analyzes; Kaplan-Meier, Chi-Square and Anova tests were used. A 3-week survival analysis was performed assuming that all sub-

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jects lived at least 1 day. The results were considered statistically significant when $p < 0.05$.

Results

A total of 24 operations were applied in 3 groups. In groups I,II and III, the number of subjects lost during surgery were 2,3 and 1 respectively (Table 1).

Table 1. Life span of subjects.

	Group I		Group II		Group III
1	1 day	**9**	-	**17**	-
2	+	**10**	+	**18**	+
3	-	**11**	-	**19**	+
4	1 day	**12**	-	**20**	11 days
5	-	**13**	+	**21**	+
6	+	**14**	2 days	**22**	13 days
7	12 days	**15**	1 days	**23**	+
8	10 days	**16**	+	**24**	8 days

+; Subjects living until the end of the study, -; Subjects died intraoperatively.

Although the average weights of subjects generally decreased, there was no significant difference between the groups at the end of the study ($p = 0.280$). Respiratory and pulse rates were compared, there was no significant difference between the preoperative and postoperative periods ($p = 0.870$ and $p = 0.514$ respectively). The oxygen saturation values were found better in early rib fixation group (group III) than the other two groups in first week and the difference was statistically significant ($p = 0.032$) (Table 2).

Table 2. Mean saturation levels of groups at the postoperative first week.

Group	Preoperative saturation (%)	Postoperative saturation at 1st week (%)
I	97	84.2
II	96	85.6
III	98	92.0
Mean	97	87.4

*P = 0.032 Statistically significant in the Kruskal-Wallis test ($p < 0.05$).

During daily follow-up, subjects in the group III were found to be more active at the early postoperative period. Daily activity, food/water interest and pain posture were better in the group III than the other two groups.

Healing of fractured ribs was followed by chest x-ray. In group I, at the third postoperative week, it was observed that fractures were not healed and there was a significant fracture line. At postoperative 7th week there was a minimal fracture healing with callus. In group III, the fixed ribs were found to heal properly without significant callus tissue in the chest x-ray even at the postoperative first week. Also it is seen that unfixed ribs healed with significant callus tissue (Figures 2a,2b).

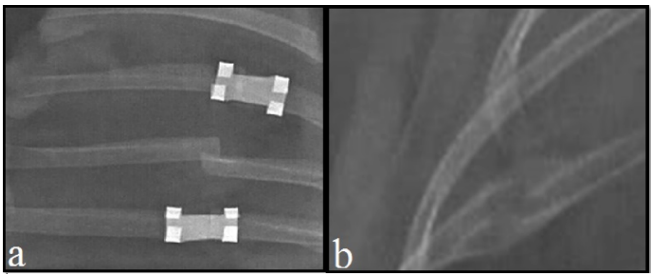

Figure 2a. Fixed and unfixed ribs in x-ray, **b.** Significant callus tissue in chest x-ray.

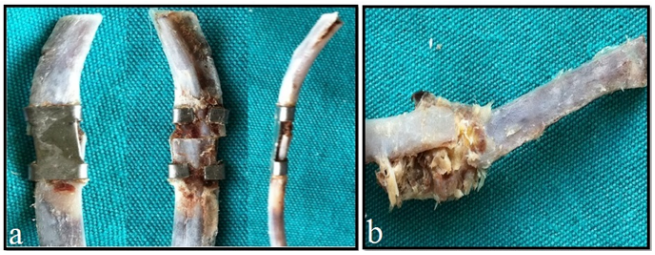

Figure 3a. Proper healing of fixed ribs, **b.** Deformed rib because of soft tissue migration.

In the third group (early fixation model), the estimated life expectancy was 14.6 days; in the group II (late fixation model) the estimated life expectancy was 8.6 days; the estimated mean life span in the first group was 8.5 days.

There was no statistically significant difference between the two groups when compared with the groups Chi-square test ($p = 0.750$, $p = 0.224$, $p = 0.402$ respectively). However, it was accepted that the third group was clinically significant because the average life span was higher than the other groups (Table 3).

Table 3. Mean survival of groups in Kaplan-Meier analysis.

Group	Estimated life span (Day)	Standard error	Chi-square test in binary groups (p)
I	8.5	2.937	P = 0.750 (I-II) P = 0.224 (I-III)
II	8.625	3.391	P = 0.402 (II-III) P = 0.750 (II-I)
III	14.625	2.524	P = 0.224 (III-I) P = 0.402 (III-II)
Mean	10.583	1.812	

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The subjects were followed up for daily food and water consumption. The average weight of the first group before surgery was 3230 g; second group 3133 g; the third group was identified as 3770 g. In general, all groups were found to have weight loss. At the end of the study, the average weight of the subjects in the first group was 2830 g; the average weight of the subjects in the second group was 2965 g; the average weight of the subjects in the third group was 3414 g. Weight losses calculated as grams per day and percentages, differences compared with Kruskal-Wallis test. There was no significant statistical difference between the groups ($p = 0.280$).

The mean saturation value of the subjects in the first group before surgery was 97%, respiratory rates 99/min, heart pulse was detected as179/min. The mean saturation value of the subjects in the second group were 96%, respiratory rate was 139/min, pulse rate was 237/min, In the third group, the preoperative saturation values were 98%, respiratory rates were 124/min, and pulse rates were 159/min.

The clinical findings of the subjects, the saturation values and respiratory and heart pulse rates, were recorded weekly. Averages of clinical findings and differences between and within groups were assessed by One-way ANOVA and Kruskal-Wallis tests. There was no statistically significant difference between the groups ($p = 0.870$ and $p = 0.514$ respectively).

There was a significant difference between the groups only in the saturation levels at first week. In the Kruskal-Wallis test, the mean saturation levels of the third group (early fixation group) were statistically better than the other groups ($p = 0.032$) (Table 2).

CBC (Hgb, Hct, WBC, RBC and PLT counts) and ABG (pH, pO2, pCO2, cHCO3, cHB, sO2, cK, cNA, cCA, cGlu, cLac, cBil) analyzes of subjects were evaluated by Kruskal-Wallis and Wilcoxon tests. There was no statistically significant difference between preoperative and postoperative results ($p = 0.165$-1.00).

Discussion

In our study, the differences between the postoperative first week saturation levels were statistically significant ($p = 0.032$). Group III's (early fixation model) results were better than the other groups. Similar results were obtained in studies in the literature. Preoperative and postoperative results of patients who underwent rib fixation due to flail chest were compared for saturation values, decrease in incidence of pneumonia, time to return to normal life, FVC values, chest wall function and cosmetic appearance were found to be better who underwent surgery [14-17].

A clinically significant result in our study was the survival of the subjects. A three-week survival analysis, in which subjects were assumed to live at least one day; mean survival in the group III (early fixation) was better than the other groups. Although survival rates were clinically significant in the group III (early rib fixation), the differences between the groups were not statistically significant ($p = 0.750$, $p = 0.224$, $p = 0.402$ respectively)

It was seen that the subjects in the group III returned to their normal eating and drinking habits during at the first week. They were more active, and it is observed that they had less pain than the others. We think the health status of the group III is better than the other groups. There are texts in the literature recommending rib fixation to reduce the pain of the patient if the fracture ends are moving in multiple and displaced rib fractures, even if they do not have flail chest [18].

We observed that displaced rib fractures did not heal properly due to the penetration of connective tissue between the fractured ends. This also caused a deformity in the chest wall.

There are also disagreements about the timing of the surgical treatment. Some authors performed surgical treatment within 36-48 hours after trauma, some have undergone surgical treatment on the fifth day of trauma [14,15]. But common view among authors is that surgery should not be applied when there is contusion in the lung, head trauma or major organ injury after trauma [13,19].

According to some authors, early-stage surgery causes removal of the hematoma in the fracture line and delays in fracture healing [20,21]. In a study on rabbits, it was indicated that the callus in the fractured area of the subjects which had been fixed on the 10^{th} day after trauma was more stable [22]. However, in our study, it was observed that fracture healing was better in the early fixation group.

In conclusion, considering today's operative techniques and minimally invasive approaches, in patients with multiple and displaced rib fractures without lung contusion and major organ injury, it is appropriate to perform rib fixation surgery before complications occur.

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Declaration of conflicting interests

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Original Article

Do we need a new SUVmax threshold value for the evaluation of mediastinal lymph nodes?

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ABSTRACT

Background: Mediastinal lymph node involvement is the most important factor determining the treatment and the prognosis with non-small cell lung cancer (NSCLC). In our study, the role of PET-CT was assessed in the evaluation of intrathoracic lymph node involvement in patients with preoperative NSCLC.

Materials and Methods: The study included 510 cases selected according to the criteria identified between January 2009 and July 2011. PET-CT staging and thorax-CT, size of lymph nodes, histological type of tumor, mediastinal lymph nodes taken and the pathological results were assessed.

Results: SUVmax cut-off value was taken as 2.5 for the metastatic analysis of lymph nodes in PET-CT and N1 and N2 lymph node stations were evaluated. Sensitivity for the N2 lymph node stations, was 74.7%, specificity 49.4%, Positive Predictive Value 25.4%, Negative Predictive Value 89,.5% and accuracy 54.1% ($p < 0.001$). Following the statistical analysis, the new SUVmax cut-off value for the N1 lymph node groups was calculated as 3.34, and for N2 lymph node groups 5.6. Based on the new SUVmax cut-off value for N2 lymph node groups, the sensitivity of PET-CT was calculated as 43.2%, specificity 94.4%, PPV 64.1%, NPV 87.8% and accuracy 84.9% ($p < 0.001$).

Conclusions: Calculating a new cut off value of SUVmax all around the world would increase the NPV of PET-CT and so it would reduce to use of invasive methods. PPV of PET-CT is still not at an acceptable level, so positive results of PET-CT for mediastinal lymph node staging should be confirmed with invasive diagnostic techniques.

Keywords: non-small cell lung cancer, lymph node, PET-CT, staging

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Introduction

Lung cancer, with increasing incidence and mortality rates, is one of the most important health problems in the world and almost one third of deaths from cancer are due to lung cancer. Only 15% of the patients can survive for five or more years after being diagnosed [1].

Half of the patients diagnosed with non-small cell lung cancer have mediastinal lymph node involvement and less than 33% are suitable for surgical resection [1]. In order to increase the success rate of surgical treatment, early diagnosis is crucial. For accurate staging of NSCLC, the location and the size of the primary tumor [T factor], regional lymph nodes [N factor] and distant metastasis [M factor] need to be identified. For this aim, Positron Emission Tomography (PET-CT) has started to be used widely in addition to the scanning methods [2].

In patients without distant metastasis, mediastinal lymph node involvement is the most important factor that determines treatment and prognosis. Therefore, accurate evaluation of mediastinal lymphatic metastasis is crucial in the preoperative stage [1,3]. Thorax-CT which is used as the initial method in the identification of metastatic mediastinal lymph node, has limited sensitivity and specificity in showing metastasis in enlarged lymph nodes [4]. On the other hand, mediastinoscopy which is the "gold standard" with excellent sensitivity and specificity rates in mediastinal staging has the disadvantage of being invasive.

The use of PET in patients with NSCLC that shows biological activity of tumor cells has increased in recent years. According to the existing studies, PET-CT is better than thorax-CT in mediastinal staging of NSCLC and it can reduce the use of invasive methods in detecting mediastinal lymph node metastasis. PET-CT is used for diagnosis, staging, restaging and follow up in NSCLC [5-7].

The aim of this study is to determine sensitivity, specificity, negative predictive value, positive predictive value and accuracy rates of PET-CT in the detection of metastatic intrathoracic lymph nodes in patients with NSCLC, through a comparison of PET-CT findings for intrathoracic lymph nodes and histopathological examination results obtained through invasive procedures. It also aims to calculate a new SUVmax cut-off value since SUVmax values in mediastinal lymph nodes increase due to bacterial, granulomas and fungal infections, which are common in Turkey, as well as due to malignancy.

Materials and Methods

The patients who were diagnosed with NSCLC and who underwent thorax-CT and PET-CT, and surgery for treatment and/or staging between January 2009 and July 2011 were prospectively reviewed. The study included all surgical cases that underwent histopathological examination apart from fine needle aspiration biopsy. 28 patients out of 538, who underwent chemoradiotherapy were excluded from the study.

Preoperative assessment of all patients included anamnesis, physical examination, respiratory function tests, electrocardiography, blood biochemistry and hemogram tests, coagulation tests, postero-anterior and lateral lung graphics, thorax-CT and PET-CT. All patients whose tumor size was bigger than 3cm underwent cranial MRI for preoperative staging. Tests and invasive procedures were performed based on TNM staging. Age, gender, preoperative diagnostic tests, location of the mass, enlarged intrathoracic lymph node on thorax-CT (>1cm), SUVmax values of masses and all intrathoracic lymph nodes in PET-CT, operations performed, lymph nodes which were sampled/excised in operation, size of the tumor lesion, histopathological examination results of sampled lymph nodes and tumor type of all patients were recorded in the database.

The areas of FDG accumulation outside normal biodistribution was identified through an evaluation of the F-18 FDG PET-CT scans. The SUVmax values were calculated.

Statistical Analysis

The statistical analysis of the data was conducted with the SPSS for Windows 11.5. Continuous variables were summarized by mean and standard error or by median (smallest-largest) and categorical variables were summarized by frequency and percentage.

Pearson's Chi-Square test and Fisher's exact test were used to assess the significance of thorax-CT results and PET-CT results in detecting metastatic and non-metastatic lymph nodes according to the histopathological results.

Using Pearson's Chi Square or Fisher's Exact tests, thorax-CT results and PET-CT results with SUVmax cut-off of 2.5 were compared for every lymph node station to assess whether they are determinate in differentiating metastatic and non-metastatic lymph nodes according to histopathological results. Sensitivity, specificity, positive and negative predictive values and accuracy rates were calculated to assess the diagnostic indicators.

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The areas under the ROC curve were calculated to determine whether PET-CT SUVmax values for every lymph node station produce statistically significant results in predicting metastatic and non-metastatic lymph nodes compared with the histopathological results. Maximum SUVmax values for N1 and N2 lymph node groups were used as a base. When the area under the curve was deemed significant, the best cutoff value was calculated using Youden Index. For each cutoff point, sensitivity, specificity, positive and negative predictive values and accuracy rates were calculated.

Logistic regression analysis was undertaken to assess the role of thorax-CT and PET-CT results in differentiating metastatic and non-metastatic lymph node groups. Odds ratio and 95% confidence intervals were calculated for both examination results. Spearman's correlation test was used to assess the presence of any significant correlation between continuous variables. Kruskal Wallis test was used to assess any significant change in SUVmax values according to the tumor types. When Kruskal Wallis test results revealed significant change, Conover's multiple comparison method was used to identify the causes of the difference. P values less than 0.05 were considered significant.

Results

The study included 510 patients diagnosed with preoperative NSCLC, who underwent thorax-CT and PET-CT, and surgery for staging/treatment between January 2009 and July 2011. 459 of the patients (90%) were male and 51 of them (10%) were female. Their ages ranged between 26 and 87 with a mean age of 59.2 + 9.0.

A diagnosis of NSCLC was made preoperatively for 263 patients (51.5%) by transthoracic fine-needle aspiration biopsy, for 245 patients (48.1%) by bronchoscopic biopsy and for 2 patients (0.4%) by video-assisted thoracoscopic biopsy.

83 patients (16.3%) were diagnosed with diabetes mellitus. Since the presence of DM did not have any significant correlation in evaluation of the PET-CT results, the patients underwent scan according to their pre-scan blood glucose levels. The mean blood glucose level was 103mg/dL (80-150mg/dL).

The patients who underwent neoadjuvant chemoradiotherapy were not included in the study.

Among 510 patients who underwent surgery for staging and/or treatment after diagnosed with NSCLC, lobectomy was performed for 284 patients (55.7%), pneumonectomy for 103 patients (20.2%), wedge resection for 8 patients (1.5%), segmentectomy for 2 patients (0.4%), exploration for 1 case (0.2%), sleeve resection of the left main bronchus for 1 case (0.2%) and mediastinoscopy for 111 patients (21.7%).

In the analysis of tumor localizations, right lung tumor lesion was detected in 286 patients (56%) and left lung tumor lesion was detected in 224 patients (44%). 132 of the right lung tumors (25.8%) were in the upper right lobe, 22 of them (4.3%) were in right middle lobe and 61 (11.9%) were in lower right lobe, and 71 (13.9%) were in the hilar region.

The size of the masses ranged between 0.4 and 20 cm with a mean size of 4 cm. SUVmax value of masses ranged between 0 and 42.8. Mean SUVmax value of the masses was calculated as 12.6.

The distribution of the tumors according to histopathologic type were squamous cell carcinoma in 229 patients (44.9%), adenocarcinoma in 162 patients (31.8%), adenosquamous carcinoma in 36 patients (7.1%), large cell carcinoma in 17 patients (3.3%) and sarcomatoid carcinoma in 12 patients (2.4%). The number of patients, who were not classified into a type, was 54 (10.6%) and these patients only underwent mediastinoscopy.

The role of PET-CT in determining the situation of intrathoracic lymph nodes and mediastinal staging in NSCLC was assessed for every station one by one. In addition, general statistical analysis was conducted for N1 and N2. N1 lymph node stations which were assessed as non-metastatic in PET-CT and histopathologically examined are 191. 160 of these patients had non-metastatic. N1 lymph nodes and 31 of them had metastatic N1 lymph nodes. There were 190 patients assessed as metastatic in PET-CT and examined. Pathological results showed that 120 of these patients had non-metastatic N1 lymph nodes and 70 of them had metastatic N1 lymph nodes. Statistical analysis of the results showed that sensitivity of PET-CT in NSCLC was 69.3%, specificity 57.1%. PPV 36.8% NPV 83.8% and accuracy 60.4% ($p < 0.001$) (Table 1).

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Table 1. Diagnostic performance rates for the PET-CT (comparison of PET-CT and pathological results).

Lymph node	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p-value
N1	69.3	57.1	36.8	83.8	60.4	< 0.001
N2	74.7	49.4	25.4	89.5	54.1	< 0.001

PPV: Positive Predictive Value NPV: Negative Predictive Value

According to the PET-CT scans of N2 lymph node stations, 228 patients had SUVmax values lower than 2.5 were assessed as non-metastatic and they underwent histopathological examination. According to the pathological results of these patients, lymph nodes were non-metastatic in 204 patients and metastatic in 24 of them. The number of patients, who had metastatic N2 lymph node station in PET-CT and examined was 280. According to the pathological results, lymph nodes in 209 of these patients were non-metastatic and metastatic in 71 patients. Following the assessment of N2 lymph node stations; sensitivity of PET-CT in identifying the situation of lymph nodes was calculated as 74.7%, specificity 49.4%, PPV 25.4%, NPV 89.5% and accuracy as 54.1% ($p < 0.001$) (Table 1).

ROC analysis was conducted and the areas under the ROC curve were calculated in order to assess whether PET-CT SUVmax values for every lymph node station can have statistically significant results in predicting metastatic and non-metastatic lymph node groups compared with the histopathological results. ROC analysis was not conducted for the No 3 lymph node station since it did not have statistically significant results. The maximum SUVmax for the relevant stations were accepted as SUVmax for N1 and N2 respectively. When the area under the curve was deemed significant, the optimal cutoff point was calculated using Youden Index. Following the statistical analyses, a new SUVmax cut-off value was calculated for N1 and N2 lymph node groups for every lymph node station.

By using ROC analysis and Youden Index in N1 and N2 lymph node groups, a new SUVmax cut-off value was calculated which could be interpreted as metastatic involvement in PET-CT. The new SUVmax threshold for N1 lymph node group was 3.34, and for N2 lymph node group was 5.605 (Table 2).

Table 2. The best cut-off value of SUVmax for N1 and N2 lymph node groups.

Lymph node	Area under the ROC Curve	%95 Confidence Internal	P-value	Best Cutoff Value
N1	0.666	0.600-0.732	<0.001	3.34
N2	0.716	0.650-0.781	<0.001	5.605

Following the statistical analysis, sensitivity, specificity, PPV, NPV and accuracy of PET-CT in detecting metastatic and non-metastatic lymph nodes were recalculated according to the new SUVmax cut-off values for N1 and N2 lymph node groups.

The number of patients who had values below the new SUVmax cut-off value of 3.34 for N1 lymph node stations in PET-CT, which were identified as non-metastatic and histopathologically examined were 269. 221 of these patients had non-metastatic N1 lymph nodes and 48 of them had metastatic N1 lymph nodes. There were 112 patients whose SUVmax value in PET-CT was 3.34 or higher and who were identified as metastatic. According to the pathological results, 59 of these patients had non-metastatic N1 lymph nodes and 53 of them had metastatic lymph nodes. Statistical analysis of the results showed that sensitivity, specificity, PPV, NPV and accuracy of PET-CT in assessing N1 lymph node stations in NSCLC patients according to the new SUVmax cut-off value were respectively 52.5%, 78.9%, 47.3%, 82.2% and 71.9% ($p < 0.001$) (Table 3).

Table 3. Diagnostic Performance of the PET-CT based on the new SUVmax cut-off value (comparison of PET-CT and pathological results).

Lymph node	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	P-value
N1 (3.340)	52.5	78.9	47.3	82.2	71.9	< 0.001
N2 (5.605)	43.2	94.4	64.1	87.8	84.9	< 0.001

PPV: Positive Predictive Value NPV: Negative Predictive Value

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The number of patients, who had values below the new SUVmax cut-off value of 5.605 for N2 lymph node stations in PET-CT and who were identified as non-metastatic and histopathologically examined were 444. According to the pathological results, 390 of these patients had non-metastatic lymph nodes and 54 of them had metastatic lymph nodes. The number of patients who had N2 lymph nodes station with PET-CT SUVmax value of 5.605 or higher, and who were identified as metastatic and histopathologically examined were 64. According to the pathological results, 23 of these patients had non-metastatic lymph nodes and 41 of them had metastatic lymph nodes. Following the evaluation of N2 lymph node stations, sensitivity, specificity, PPV, NPV and accuracy of PET-CT in determining the situation of lymph nodes according to the new SUVmax cut-off value for N2 lymph nodes were respectively, 43.2% 94.4%, 64.1%,87.8% and 84.9% ($p < 0.001$) (Table 3).

Following the analysis of the data for all patients, a new PET-CT SUVmax cut-off value in detecting metastatic intrathoracic lymph nodes was calculated. The new SUVmax cut-off value was 4.5. According to this new value, sensitivity, specificity, PPV, NPV and accuracy of PET-CT in mediastinal staging in NSCLC were respectively 47.9%, 86.7%, 55.7%, 90% and 78.4%.

Diagnostic performance values of PET-CT SUVmax cut-off value of 2.5 and the new SUVmax cut-off value were compared in Table 4.

Table 4. Comparison of PET-CT based on SUVmax cut-off value 2.5 and the new SUVmax cut-off values.

Lymph node	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
PET SUVmax 2'5 N1	69.3	57.1	36.8	83.8	60.4
PET SUVmax new value N1	52.5	78.9	47.3	82.2	71.9
PET SUVmax 2'5 N2	74.7	49.4	25.4	89.5	54.1
PET SUVmax new value N2	43.2	94.4	64.1	87.8	84.9

PPV: Positive Predictive Value NPV: Negative Predictive Value

Discussion

Staging based on TNM staging system is fundamental in planning treatment and predicting prognosis in NSCLC. The most important point is to identify the patients suitable for surgical resection and inoperable patients who could benefit from chemotherapy and/or radiotherapy.

Primary mediastinal lymph node staging can be done with several techniques including imaging techniques, endoscopic techniques and surgical techniques. PET-CT is a special diagnostic tool in diagnosis, staging and follow up of the cancer patients compared to other scanning methods. In the evaluation of mediastinal lymph node metastasis, PET/CT has a higher accuracy rate when compared with thorax-CT and its specificity ranges are between 80-95%, negative predictive value (NPV) is 84-100%, positive predictive value (PPV) is 60-93% [8].

According to the 2003 meta-analysis of Toloza et al. on diagnostic performance of noninvasive mediastinal staging methods based on 20 studies with 3438 patients, sensitivity of thorax-CT in detecting mediastinal lymph nodes metastasis was 57%, specificity 82%, PPV 44% and NPV 17% [7]. In our study, the sensitivity of thorax-CT in detecting metastatic lymph nodes is 75.7%, specificity 41%, PPV 27.3%, NPV 85% and the accuracy 48.4%. While the sensitivity and the NPV of thorax-CT in our study is similar to the other studies, the specificity and the PPV are lower. We believe that this is due to the bigger size lymph nodes caused by infectious and granulomas diseases, which are common in Turkey.

According to the meta-analysis of Toloza et al based on 5687 patients published in 2003, the sensitivity of mediastinoscopy which is considered as gold standard in mediastinal staging was 84%, specificity 100%, PPV 100% and NPV 91% [9]. However, despite these high diagnostic performance rates, the mortality and morbidity rates, albeit low, bring up the necessity of using less invasive or non-invasive staging methods instead of mediastinoscopy due to its disadvantages of being an invasive method and limited number of lymph node sampling.

PET-CT is widely used compared to other non-invasive mediastinal staging methods. There are many studies conducted between 1990 and 2000 comparing the performances of thorax-CT and PET-CT in detecting mediastinal lymph node metastasis and the majority

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of these studies concluded that PET-CT is more effective than thorax-CT [7,10,11]. According to the Burry's study published in 1997, the specificity of PET-CT in detecting mediastinal lymph node metastasis is 100%, PPV 100% and NPV 96% [12]. Owing to its high accuracy rates and its being non-invasive, it has been argued that PET-CT could replace mediastinoscopy.

An analysis of these initial studies shows that the number of patients studied are not sufficient, and in some studies mediastinoscopy was not performed for all patients or some patients included in the study were not diagnosed with lung cancer. The studies conducted in the following years did not confirm those initial results. For example, while the sensitivity rate of PET in detecting mediastinal lymph node metastasis was 64%, specificity 77%, PPV 44% and NPV 88% according to the study conducted by Gonzales-Stawinski in 2003 based on 202 patients; according to REED CE's [14] 2003 study based on 302 patients [13] sensitivity was 61%, specificity 84%, PPV 56% and NPV is 87%. On the other hand, Toloza reports that sensitivity of PET in detection of metastatic mediastinal lymph nodes was 84%, specificity 89%, PPV 79% and NPV 93% in his review study published in 2003 based on 1045 patients [7].

Inflammatory diseases are among the reasons for false positive results of PET-CT and FDG accumulation might be seen in regions where there is active inflammation. This activity is caused by macrophage in inflammated regions and increased glucoses uptake in inflammated cells. The reason for low specificity rates, which can be defined as the rate showing lymph nodes in PET-CT are not metastatic, in patients who does not have metastatic intrathoracic lymph nodes in reality is believed to be caused by mediastinal involvement in PET-CT because of benign infectious (tuberculosis, histoplasmosis) and inflammatory diseases. Due to the low PPV rates in the evaluation of mediastinal lymph nodes in PET-CT, there is a need for cell diagnosis to show metastasis. Mediastinoscopy or other invasive mediastinal staging methods can be used. However due to the high NPV rates, if there is no involvement in mediastinal lymph nodes in PET-CT surgical treatment can be planned without invasive staging. Graeter et al. argue that in cases of negative mediastinal lymph nodes in PET-CT in NSCLC patients, mediastinoscopy can be ignored [15].

In our analysis based on SUVmax value 2.5 in detecting N1 disease, the sensitivity of PET-CT was calculated as 69.3%, specificity 57.1%, PPV 36.8% and NPV 83.8% and accuracy 60.4%. In identifying N2 disease, sensitivity, specificity, PPV, NPV and accuracy rates were respectively, 74.7%, 49.4%, 25.4%, 89.5% and 54.1%. In identifying metastatic intrathoracic lymph nodes, sensitivity was calculated as 72%, specificity 53.3%, PPV 31.1%, NPV 86.7% and accuracy 57.3%. In comparison to other studies in the literature, our study had lower specificity and PPV rates and the other diagnostic performance rates were similar.

The new SUVmax cut-off value calculated following the statistical analysis of the patients was 4.5 and sensitivity, specificity, PPV, NPV and accuracy rates based on the new value were respectively 47.9%, 86.7%, 55.7%, 90% and 78.4%. Since the specificity and PPV based on the new SUVmax cut-off value was lower, it might lead to false negative results in evaluation of metastatic lymph nodes that have low involvement. Benjamin et al calculated a new cut-off value in their study and argued that in patients whose SUVmax value is lower than 5.3 and which do not have central tumor and N1 disease, thoracotomy can be performed directly without the need for invasive staging. They also argue that while PET-CT is an important and effective method compared to other non-invasive staging methods, its maximum effectiveness has decreased due to high false positive (infectious and inflammatory diseases) and false negative (micrometastasis) rates [16].

In areas with granulomas diseases, high FDG involvement can be observed in benign lesions. According to the study by Kwan in Taiwan, there is an increased FDG involvement in mediastinum in 28% normal patients [17]. Kang et al. found significant difference between the SUVmax rates of malignant lesions and benign lesions (18). SUVmax cut-off value in lymph nodes which have involvement in mediastinum was calculated as 3.4. In this study, it is argued that FDG involvement is more significant than lymph node size in thorax-CT. Our study showed that when lymph nodes measuring 1cm or more in the short axis in thorax-CT were compared with mediastinal FDG involvement in PET-CT, PET-CT gave more accurate results. It was found that if lymph node size and SUVmax rate are compatible, diagnostic performance is better.

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The literature on false positive or false negative results of PET-CT is limited. The study conducted by Takamochi et al. on the basis of patients showed the false positive rate as 14% and false negative rate as 20% [19]. According to our study based on the evaluation of patients, the false positive rate was calculated as 50.6% and false negative rate as 25.3%. The reason for this higher rate of false positivity compared to other reported rates is normal considering the specific circumstances in Turkey. The higher incidence rate of infectious diseases in Turkey is influential in higher rates of false positivity.

To sum up, more studies are being conducted to find the fastest, most accurate and the least invasive methods through a comparative analysis of different mediastinal staging methods. Recent studies focused on showing the role of PET-CT in mediastinal staging. The aim is to determine whether PET-CT could be an alternative to mediastinoscopy in mediastinal staging.

In conclusion, calculating a new cut off value of SUVmax all around the world would increase the NPV of PET-CT and so it would reduce to use of invasive methods. PPV of PET-CT is still not at an acceptable level, so positive results of PET-CT for mediastinal lymph node staging should be confirmed with invasive diagnostic techniques. Invasive staging must be performed in order to verify metastasis in lymph nodes which have pathological involvement in PET-CT. However, rather than deciding on surgery solely based on PET-CT results, more accurate decisions can be taken by taking into account thorax-CT results, localization of tumor masses, cell type, and SUVmax values of the masses.

Declaration of conflicting interests

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Original Article

Granulomatous disease in patients operated due to provisional diagnosis of lung cancer

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ABSTRACT

Background: The granulomatous reaction is a response that can occur in many infective, toxic, allergic, autoimmune, neoplastic, and etiologically unknown conditions. Hundreds of different agents that can cause this response. The most common granulomatous disease in Turkey and in developing countries is mycobacterial infection-related tuberculosis. This study was carried out to show the prevalence of patients operated in our clinic due to provisional diagnosis of lung cancer and diagnosed with granulomatous disease.

Materials and Methods: 380 patients who underwent diagnostic and therapeutic videothoracoscopy or thoracotomy due to provisional diagnosis of malignancy, and were diagnosed with granulomatous disease in consequence of histopathological examination between the years of 2011 and 2016 were included in the study. Patients were examined with regard to their clinical characteristics.

Results: Granulomatous disease was detected histopathologically in 28 (7.3%) of them. The final histopathological diagnosis was tuberculosis in 20 patients (71.4%), sarcoidosis in 3 patients (10.7%), infection in 2 patients (7.1%), rheumatoid nodule in 2 patients (7.1%), and allergic angiitis in one patient (3.5%).

Conclusions: In regions where tuberculosis is frequent, such as Turkey, granulomatous diseases should be considered in the differential diagnosis of lesions suspicious for malignancy.

Keywords: granulomatous disease, tuberculosis, sarcoidosis, lung cancer

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Introduction

It is difficult to make the pathological and clinical differential diagnosis of granulomatous lung diseases. There are hundreds of different agents that can cause granulomatous diseases. These agents can be classified as bacterial, chlamydial, fungal, helminthic infections, metals, organic salts, foreign bodies, and etiologically unknown diseases. The most common granulomatous disease in Turkey and in developing countries is mycobacterial infection-related tuberculosis. These diseases may mimic malignancy. Therefore, a differential diagnosis is essential. Either transthoracic fine needle aspiration biopsy (TFNAB), endobronchial ultrasonography (EBUS), transbronchial biopsy (TBB), videothoracoscopic biopsy (VATS) or thoracotomy can be performed for the diagnosis of granulomatous lesions. In this study, we aimed to determine the incidence of granulomatous disease in patients who could not be diagnosed through TFNAB and TBB, and had a high suspicion of malignancy, who underwent surgical resection.

Materials and Methods

380 patients who were operated due to the provisional diagnosis of lung carcinoma between January 2011 and December 2016 were analyzed retrospectively. The cases were assessed according to gender, age, surgical treatment method, and results of histopathological diagnosis. In the preoperative period, patients were asked to have a posteroanterior chest X-ray (PA CXR), computed tomography (CT), pulmonary function tests (PFT), routine blood tests, and patients with a high suspicion of malignancy were asked to have PET-CT. Patients' information was analyzed retrospectively.

Results

Of 380 patients operated for diagnosis, 236 patients (62.1%) were diagnosed with intraoperative lung carcinoma, whereas 116 patients (30.5%) had other benign tumors, and 28 patients (7.3%) had granulomatous disease. The mean age was 49 (13-66); 14 patients (50%) were women and 14 (50%) were men. All 28 patients had thorax CT. The mean diameter of the masses was 2.05 ± 0.51 cm (0.5 to 4 cm). 22 patients underwent preoperative positron emission tomography (PET-CT). The mean value of SUVmax was 5.26 ± 4.25 (2.4-19).

Table 1. Demographic characteristics of the patients in the study group.

	n	%
Sex		
Male	14	50
Female	14	50
Histopathological diagnosis		
Tuberculosis	20	71.4
Sarcoidosis	3	10.7
Infection	2	7.1
Rheumatoid nodule	2	7.1
Allergic angiitis	1	3.5
Operation		
Wedge resection	22	78.5
Lobectomy	3	10.5
Incisional biopsy	2	7.1
Segmentectomy	1	3.5

Seven patients (25%) were operated via VATS, and 21 patients (75%) were operated via thoracotomy. The mass was completely excised in 26 patients (92.8%), while incisional biopsy was performed on 2 patients (7.1%). Wedge resection was performed on 22 patients (78.5%), lobectomy on 3 patients (10.7%), and segmentectomy on 1 patient (3.5%).

The final histopathological diagnosis was tuberculosis in 20 patients (71.4%), sarcoidosis in 3 patients (10.7%), infection in 2 patients (7.1%), rheumatoid nodule in 2 patients (7.1%), and allergic angiitis in one patient (3.5%). Lobectomy was performed on 2 (7.1%) patients in order to achieve complete resection due to the presence of accompanying hemoptysis and cavitary lesion, and on 1 (3.5%) patient due to frozen section examination reported to be suspicious for malignancy. Diaphragmatic laceration developed during operation in one (3.5%) patient and primary repair was performed. Prolonged air leak (longer than 7 days) was observed in 3 (10.7%) patients. Postoperative mortality was not detected.

Discussion

Granulomatous lung diseases are a heterogeneous group of disorders which have a wide spectrum of pathologies with variable clinical findings and outcomes. Precise clinical evaluation, laboratory tests, pulmonary function tests, radiological imaging including high-resolution computed tomography (HRCT), and often histopathological evaluation contribute to make the diagnosis of

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granulomatous lung diseases [1]. There are hundreds of different agents that can cause a granulomatous reaction. These agents can be categorized into bacterial (tuberculosis, leprae, salmonella, brucella, syphilis, Q fever, cat scratch disease), chlamydial (lymphogranuloma venereum), fungal (histoplasmosis, blastomycosis, coccidiomycosis), helminthic (schistosomiasis, filariasis, trichinosis) infections, metals (berylliosis, zirconium), organic salts, foreign bodies (silicosis, asbestosis), and etiologically unknown diseases (sarcoidosis, Crohn's disease, Wegener's granulomatosis, primary biliary cirrhosis). The most common granulomatous disease in Turkey and in developing countries is mycobacterial infection-related tuberculosis [2,3]. The presence of a large number of macrophages and lymphocytes in granulomatous diseases is associated with high uptake of 18F-fluoro-2-deoxy-d-glucose (FDG) mimicking lung cancer on PET imaging [3,4]. The radiological characteristics of granulomatous diseases, therefore, may not be distinguishable from lung carcinoma [4,5]. In our study, 236 (62.1%) of 380 patients who were operated due to provisional diagnosis of malignancy were diagnosed as lung carcinoma, whereas 28 (7.3%) patients were diagnosed as granulomatous disease. Twenty-two of the 28 patients were found to be at high risk of malignancy and PET-CT was requested, and pathologic FDG uptake was observed in 18 patients.

Methods such as CT-guided TFNAB, TBB, VATS, and biopsy via thoracotomy could be performed to take histopathologic samples [6]. In our clinic, to make a diagnosis, seven of 28 patients who could not be diagnosed through TFNAB and TBB underwent VATS and 21 patients underwent thoracotomy.

Cases in which lobectomy was performed due to cavitary lesions and hemoptysis have been reported in the literature [7]. In our clinic, lobectomy was performed in one (3.5%) patient since malignancy could not be eliminated and on 2 (7.1%) patients in order to achieve complete resection due to accompanying hemoptysis, as well as the presence of cavitary lesion. The most common postoperative complication in the surgery of granulomatous diseases is prolonged air leak [8]. In our series, this rate was 10.7% with 3 patients.

Tuberculosis is an important health problem in developing countries such as Turkey [9]. The most diagnosed granulomatous disease in our clinic was also tuberculosis, with a rate of 71.4%. It was observed that tuberculosis was the most common disease in this patient group. It should not be forgotten that granulomatous diseases, especially tuberculosis, might mimic malignancy and cause delays in diagnosis and treatment [10].

In conclusion, granulomatous diseases should be considered in the differential diagnosis of lesions suspicious for malignancy and patients must be carefully examined in terms of tuberculosis.

Declaration of conflicting interests

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Original Article

Analysis of risk factors in surgical treatment of lung cancer patients over 70 years of age: how effective are the cardiac risk score and age?

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ABSTRACT

Background: In this study, the age and cardiac risk factors on mortality, and complications after surgical treatment in lung cancer patients were investigated.

Materials and Methods: Between January 2014 and November 2016, 485 patients who underwent lung resections for lung cancer in our clinic, were retrospectively evaluated. Under the age of 70, 412 patients and over 70, 73 patients were grouped as group 1 and 2.

Results: Lobectomy was performed in 333 patients (80.8%), pneumonectomy in 43 (10.4%), bilobectomy in 30 (0.7%), segmentectomy in 3 (0.7%) and sleeve lobectomy in 3 (0.7%) in group 1; lobectomy in 65 (89%), pneumonectomy in 4 (5.4%), and sleeve lobectomy in 4 (5.4%) in group 2. Surgical mortality was observed in 5 patients (1.2%) in group 1 and 6 patients (8.2%) in group 2. Complications were observed in 99 patients (24%) in group 1 and 23 patients (17%) in group 2. The mean expected mortality with cardiac risk score in group 1 was 1.24 and 3.5 in group 2. The expected mortality with cardiac risk score and complication rates were tabulated as low, moderate, high and there was no statistically significant difference between score and complication ($p = 0.551$).

Conclusions: According to our study, there were no significant differences in terms of complications, morbidity, mortality and survival rates. There was only a relative increase in surgical mortality over the age of 70, so patients should be carefully treated during and after the surgery. Surgery should be the first treatment to perform in selected patients with lung cancer over the age of 70.

Keywords: cardiac risk factor, lung cancer, mortality, surgery

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Introduction

In recent years, there has been a rapid increase in population over 70 years in our country. The rapid growth of the geriatric population causes the health system to face new problems. The elevated number of the 70-year-old population increases the proportion of patients with lung cancer who underwent surgery in thoracic surgery clinics, and the risk of mortality and complications due to surgical procedures is high [1,2]. By this time in a very small number of studies were focused on patients with operable lung cancer older than 70 years of age, especially those with advanced disease. There are only a few geriatric patient-specific studies for treatment in early stages.

In this study, we evaluated the results of surgical resection of lung cancer patients and investigated the effects of preoperative cardiac risk factors on mortality and complications in patients over 70 years of age.

Materials and methods

We retrospectively evaluated 514 patients who were referred to our clinic for surgical treatment between January 2014 and November 2016, diagnosed with lung cancer. In preoperative period; total blood counts, biochemistries, electrocardiographs (ECG) were performed. Echocardiographs were performed with cardiology consultations to the patients who either had pathologic findings on ECG or were over 50 years old. Patients with diabetes and hypertension were consulted for internal medicine and the patients were operated after blood glucose and blood pressure regulations. Also all of our patients' the expected mortality (logistic score) was determined with cardiac risk score (http://www.euroscore.org/calc.html) (Table 1).

Table 1. Risk factors, definitions and weights (score).

	Definition	Score
Patient-related factors		
Age	Per 5 years or part there of over 60 years	1
Sex	Female	1
Chronic pulmonary disease	Longterm use of bronchodilators or steroids for lung disease	1
Extracardiac arteriopathy	Any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	2
Neurological dysfunction	Disease severely affecting ambulation or day-to-day functioning	2
Previous cardiac surgery	Requiring opening of the pericardium	2
Serum creatinine	>200 mmol/L preoperatively	2
Active endocarditis	Patient still under antibiotic treatment for endocarditis at the time of surgery	3
Critical preoperative state	Any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria , <10 ml/h)	3
Cardiac-related factors		
Unstable angina	Rest angina requiring i.v. nitrates until arrival in the anesthetic room	2
LV dysfunction	Moderate or LVEF 30-50%	1
	Poor or LVEF<30	3
Recent myocardial infarct	<90 days	2
Pulmonary hypertension	Systolic PA pressure >60 mmHg	2
Operation-related factors		
Emergency	Carried out on referral before the beginning of the next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta	For disorder of ascending, arch or descending aorta	3
Postinfarct septal rupture		4

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The patients with a forced expiratory volume in 1 second (FEV1) value of over 2 liters in the pulmonary function tests were operated without further pulmonary evaluation while carbon monoxide diffusion capacity (DLCO), perfusion scintigraphy, oxygen consumption capacity or exercise tests (6 minutes walk, test) were applied the other patients. If the estimated postoperative FEV1 was below 800 mL and the oxygen consumption capacity was below 15 mL/kg/min, our patients had not undergone surgery.

Patients with mediastinal lymph node involvement who were determined to be able to undergo surgical treatment were first underwent endobronchial ultrasound-guided transbronchial needle aspiration and / or mediastinoscopy. Patients with proven mediastinal metastasis were referred to the oncology clinic for adjuvant or neoadjuvant therapy. Patients without mediastinal metastasis or who had neoadjuvant therapy treated with anatomical lung resection and systematic mediastinal lymph node dissection. Ten patients who were diagnosed with lymph node metastasis by mediastinoscopy, 3 patients who were only explored with thoracotomy, and 16 patients who underwent surgery after neoadjuvant treatment were excluded from the study.

The remaining 485 patients (88 females, 397 males, mean age 59.7 years, range 9 to 82 years) composed our study group. Air leaks that lasted more than 7 days were considered as a prolonged air leak, and the deaths within 30 days after the surgery were considered as surgical mortality. Group 1 was consisted of 412 patients under the age of 70, and group 2 was consisted of 73 patients over 70 years of age.

Statistical analysis

Parametric methods were used for analysis of variables with normal distribution, and non-parametric methods were used for analysis of variables having no normal distribution. Independent sample test and Mann-Whitney U tests were used in comparison of groups among independent groups. Pearson Chi-Square and Fisher's Exact tests were used to compare categorical data. Kaplan-Meier test was used for survival analysis. Quantitative data were tabulated with mean ± SD values, and categorical data with and percent values. The data were analyzed at 95% confidence level, P values less than 0.05 are considered significant. The Statistical Package for the Social Sciences (SPSS) 21 program was used for statistical analysis. Among the groups, complications, early mortality, hospital stay, survival rates were compared.

Results

In patient groups; smoking histories were found in 350 (84%) patients in group 1 and in 50 (68%) patients in group 2. Lesion locations of the patients in group 1 were: 231 (56%) in the right lung, 181 (44%) in the left lung and in group 2: 39 (53%) in the right lung, 34 (47%) in the left lung. Lobectomy was performed in 333 patients (80.8%), pneumonectomy in 43 patients (10.4%), bilobectomy in 30 patients (7.2%), segmentectomy in 3 patients (0.7%) and sleeve lobectomy in 3 patients in group 1. Lobectomy in 65 patients (89%), pneumonectomy in 4 patients (5.4%), and sleeve lobectomy were performed in 4 patients (5.4%) in group 2 (Table 2).

Table 2. Operation procedure, lesion locations and smoking histories of our patient.

	Group 1	Group 2
Operative procedure		
Lobectomy	333 (80.8%)	65 (89%)
Pneumonectomy	43 (10.4%)	4 (5.4%)
Sleeve lobectomy	3 (0.7%)	4 (5.4%)
Bilobectomy	30 (7.2%)	
Segmentectomy	3 (0.7%)	
Lesion locations		
Right lung	231 (56%)	39 (53%)
Left lung	181 (44%)	34 (47%)
Smoking history	350 (84%)	50 (68%)

When postoperative histopathological results were analyzed, the most common tumor cell type was adenocarcinoma (45% and 52%) in both groups, while squamous cell carcinoma cell types were seen 32% in both groups.

Five of the patients in group 1 had mortalities (1.2 %), while in group 2 mortalities were found in 6 patients (8.2%). The most common causes of mortality were with the cardiac origin. In group 1, myocardial infarction was seen in 3 patients, and renal insufficiency in 2; in group 2, 3 of the patients had developed myocardial infarction, renal insufficiency was seen in 2 patients and bronchopleural fistula due to empyema and respiratory

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insufficiency in 1. 116 complications occurred in 99 patients (24%) in group 1 and 17 (23.3%) in group 2. The most common complication was the failure of the expansion in the lung after surgery in 56 patients [group 1 (n = 50) + group 2 (n = 6)]. Other frequent complications were prolonged air leak in 20 patients [group 1 (n = 18) + group 2 (n = 2)] and infection of operation wound in 14 patients [group 1 (n = 11) + group 2].

The mean hospital stay was 15 days (range 4-99) in group 1, and 15.6 days (range 5-46) in group 2. There was no statistically significant difference between them ($p > 0.05$). In both groups, the mean length of hospital stay was 14.3 days when the patients with postoperative complications were excluded. The mean duration of hospitalization for the patients with postoperative complications was 18 days.

The expected mortality (logistic score) with cardiac risk score of 412 patients in group 1 was 1.24 and the score of the seventy three patients in group 2 was 3.5. The expected mortality with cardiac risk score and complication rates were tabulated as low, moderate, high and there was no statistically significant difference between score and complication $p = 0.551$ (Table 3).

Table 3. The expected mortality with cardiac risk score and complication rates.

	Uncomplicated cases (%)	Complicated cases (%)
Low	330 (76.6%)	101 (23.4%)
Middle	37 (72.5%)	14 (27.5%)
High	2 (66.7%)	1 (33.3%)

Mean survival rates of our patients were shown on the table 4.

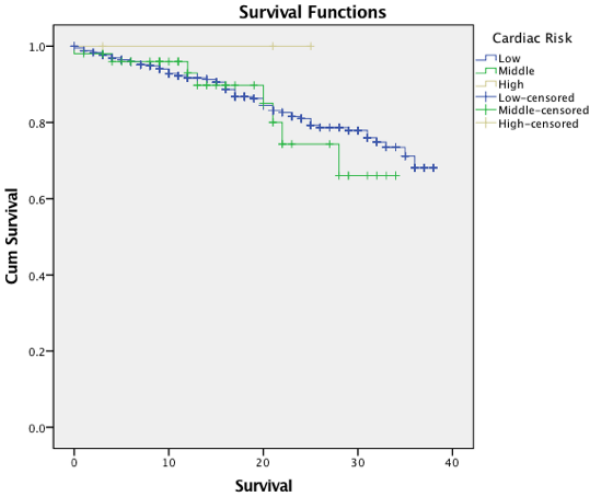
Table 4. Mean survival rates of our patients.

	Min.	Max.	Mean	Standard deviation
Survival Rates	0	38	18.24	10.478

The expected mortality with cardiac risk score and survival rates were shown on the table 5 and a Kaplan Meier survival curve was drawn by Log-rank method (Graphic 1). There was a statistically significant difference in mortality between low cardiac risk and moderate cardiac risk $p = 0.028$.

Table 5. The expected mortality with cardiac risk score and survival rates.

	Died	Alive
Cardiac risk		
Low	363	68
Middle	43	8
High	3	0
Total	409	76



Graphic 1. Kaplan Meier survival curve for the expected mortality with cardiac risk score and survival rates.

Discussion

Lung cancer is the leading cause of cancer-related deaths worldwide, and non-small cell lung cancer (NSCLC) constitutes more than 80% of lung cancers [3]. Surgery is the best-recommended treatment for patients with early stage lung cancer [4].

The median age of newly diagnosed NSCLC in the USA is 68 years, and more than 40% of newly diagnosed patients are over 70 years of age and 14% are over 80 years old [5]. Given the increasingly aging world population, it is clear that we will face more patients with NSCLC in the coming years and therefore it is frequently encountered with heart diseases, chronic obstructive pulmonary diseases, diabetes, renal dysfunctions and other medical problems. For this reason, the choice of treatment for patients over 70 years of age is becoming increasingly important [6]. In our study, 73 (15%) of 485 patients who were older than 70 years of age were diagnosed as lung cancer and underwent surgical treatment. It was found that, the number of patients in this age group increased when compared with the rates in

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the past years. However, compared to other studies, it is possible that the low numbers of elderly patients with lung cancer treated surgically in our country, might be due to the high population of young people, the desire of elderly patients and their relatives to refuse surgery, and the sensitivity of surgeons to do the surgery.

In our study, no patients were evaluated as inoperable due to advanced age. Lymph node dissection was performed with complete lung resection for all patients. None of the patients underwent limited lung resection. From the point of view of surgery, pneumonectomy was applied to 10% of patients under the age of 70, and to 5% of patients over 70 years of age. This difference may be due to limited respiratory capacity in patients over 70 years of age and consequently the decision to perform pneumonectomy was taken cautiously. When planning surgical treatment in elderly patients, we should consider the following: the mortality rate of the surgeon to be performed should be acceptable, and should not exceed 4% for lobectomy and 8% for pneumonectomy [7,8]. Dalwadi et al. [9] stated that their data with elderly patients, stereotactic body radiation therapy (SBRT) replaced surgery as the most used modality for early stage NSCLC. Selecting elderly patients with comorbidities appropriately, surgical outcomes declined with age but the SBRT outcomes did not.

In the literature, after a lung resection, associated pulmonary complications such as prolonged air leak, pneumonia, pulmonary embolism, respiratory failure, and bronchopleural fistula have been reported more frequently [4,10-12]. Among cardiac complications, rhythm disorders were reported between 3.8% and 37% [13]. Toker et al. reported that cardiac complication rates were 20% higher than the other series, and age, sex, and past myocardial infarction after pulmonary surgery have not been associated with major complications and mortality [14]. In another study, no significant relationship was found between age and postoperative pneumonia [2]. Another study reported that cardiopulmonary complications were more common in the elderly than in younger patients, but the only difference for risk of death between the two groups was reported as pulmonary complication. Therefore, elderly patients should be evaluated in detail before surgery [2,4]. Some authors have advocated the preoperative evaluation of patients over the age of 60, the need for cardiologic examination, whether symptomatic or asymptomatic [2]. In our study, we performed ECG with cardiology consultations and echocardiography examination, pulmonary function tests or advanced tests for all patients over 50 years old, and after evaluating the patient was appropriate, anatomical lung resections were performed. The complication rate was 23.3% in group 2 and 24% in group 1, but this difference was not significant between the two groups. 116 complications occurred in 99 patients in group 1 and 17 in group 2. The most common complication was postoperative expansion failure of the lung (n = 56). Other frequent complications were prolonged air leak in 20 patients and infection of operation wound in 14 patients.

The morbidity rate after anatomical pulmonary surgery was reported to be about 30%, after pneumonectomy was between 15% and 75%, and was found to be higher than in other lung resections; cardiac complications, most often rhythm disorders were reported between 3.8% to 37%, and the incidence of arrhythmia in elderly patients were reported 10,7% in the series [10,14]. The cause of arrhythmia is not exactly known. The possible causes are mediastinal shift, hypoxemia, and abnormal blood pH. However, the well-known reputation is, arrhythmia formation occurs in elderly patients, after a coronary artery disease and extended resections, especially after intrapericardial pulmonary vascular ligation [10]. Risk of life-threatening pulmonary embolism following surgery includes increased physiological changes in the cardiovascular system and respiratory system related to the age, diabetes, kidney and liver diseases [7,15–17]. For these reasons, a number of studies have been carried out to explain whether morbidity and mortality rates after geriatric patients treated with surgery for lung cancer are affected by age.

In surgical treatment, the known mortality rate for pneumonectomy is between 3-12%. The mortality rate for lobectomy is 1-4% and it is half of the mortality rate of pneumonectomy [10]. Roxburgh et al. [11] reported that mortality was higher in older patients after pneumonectomy, but the difference was not significant. Dyszkiewicz et al. [18] reported mortality of pneumonectomy in elderly patients was 17% and mortality was not detected in the same group with lobectomy or wedge resection. The mortality rates for patients over

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70 years of age were reported as 2.4% for lobectomy, 12.5% for pneumonectomy, and 4.2% for lobectomy in patients with lung cancer over 80 years old [10]. Rostad and Mark [19] found that the mortality rate doubled between the ages of 70-79. Different results have been reported regarding postoperative mortality and morbidity rates in elderly patients in general. Many authors have stated that the risk is higher in older people, but recent studies have shown that the mortality rate is acceptable [2] Careful patient selection is very important to reduce the expected higher mortality and morbidity rate. Suemitsu et al. [20] have indicated that surgical treatment is useful for selected elderly patients who may be able to tolerate surgery and achieve complete resection [20,21]. In our study, surgical mortality of group 1 was found 1.2% (n = 5), while in group 2.2% (n = 6). Mortality rates are better in group 1 when compared with the literature, and in group 2 are in the same range. In this case, there should be a more experienced team in group 2 and more careful operations should be done.

The survival rate should be increased after surgery and the quality of life should not deteriorate after surgery [8]. Onaitis et al. [22] had stated that, thoracoscopic approach is associated with improved long-term survival in elderly patients in comparison to thoracotomy, although it is difficult to explain the advantages of long-term survival. Procedure choice and approach choice is complex and cannot be easily decided. In our study, with carefully selected patients over 70 years of age with NSCLC, there was no significant increase in complication rates and survival rates.

Evaluation with the cardiac risk score showed that, age-related score were found to be higher in the group with over 70 years of age, but there was no statistically significant difference between the groups in terms of survival, complications and other parameters except early mortality. As the number of these studies increase, the age factor for cardiac risk scoring can be reevaluated. Due to the increase in early mortality in patients over 70 years of age, careful follow-up and treatment of the patients during and after the operation should be performed and coordinated multidisciplinary and necessary treatments should be given to the patients. New studies has begun for geriatric patients for the last 10 years, but in these studies the majority of patients are in the early 70's and the number of patients over 80 is low [23,24]. According to the new age groups of the World Health Organization, between the ages of 66-79 were determined as middle ages and between 80-99 as elderly. For that reason, more studies should be done in the group of patients over 70 years old.

As a conclusion, in the presence of early stage pulmonary malignancy, surgical treatment should be considered primarily in patients over 70 years of age. Being 70 years or older should not be a single contraindication for surgery, or indications for limited resection alone. We believe that this age group of patients may also be treated surgically with an acceptable risk level.

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Case Report

Pulmonary alveolar proteinosis: a case report

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by accumulation of material in the alveoli of the lungs. It is generally diagnosed in middle-aged men. The most common complaints are cough and dyspnea. Characteristic radiological findings of PAP include nodular infiltration with a tendency to merge and ground glass density, septal thickening and resemblance to paving stone. Typical findings include periodic acid-Schiff (PAS) stain positive materials in the alveolar proteinosis, milky appearance of bronchoalveolar lavage (BAL), interstitial opacities, thickened interlobular septa, and patchy central or peripheral ground-glass opacities in the lung parenchyma in the chest CT. The most effective proved treatment is whole lung lavage. The aim of the treatment in PAP cases is to restore the alveolar gas exchange by removing excess surfactant accumulated in the alveoli.

Keywords: alveolar proteinosis, bronchoalveolar lavage, dyspnea

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Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by accumulation of material in the alveoli of the lungs, which could take primary and secondary forms [1]. It is generally diagnosed in middle-aged men [2]. Typical findings include periodic acid-Schiff (PAS) stain positive materials in the alveolar proteinosis, milky appearance of bronchoalveolar lavage (BAL), interstitial opacities, thickened interlobular septa, and patchy central or peripheral ground-glass opacities in the lung parenchyma in the chest CT. The most effective proved treatment is whole lung lavage [3].

Here we present a case of pulmonary alveolar proteinosis, admitted with symptoms of cough and progressive dyspnea, diagnosed with BAL and had atypical scan results, along with a review of literature.

Case Report

A 70-year-old man admitted to our clinic with complaints of cough and progressive dyspnea of five months duration. According to his medical records, he was not able to meet his basic daily needs and walk without support due to dyspnea. In addition to non-productive cough and dyspnea, he suffered from loss of appetite and fatigue. The findings on physical examination included cyanosis in lips, intercostal recession, decreased breath sounds and low levels of rhonchus. Oxygen saturation was measured as 75% using non-invasive methods.

He was hospitalized and empiric antibiotherapy, inhaler and parenteral corticosteroids, diuretic treatment was started. Chest CT showed increased ground glass densities at periphery of both lung parenchyma, particularly in the superior segment of the lower lobe and upper lobes (Figure 1).

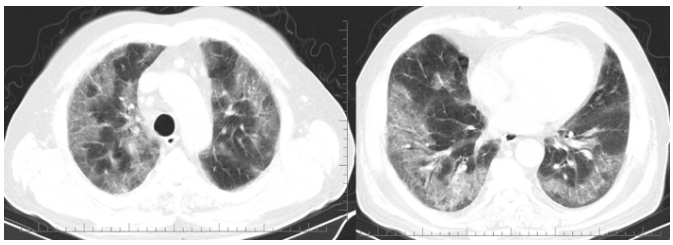

Figure 1. Increased ground glass density in the superior segment of the lower lobe and upper lobes.

Despite nasal oxygen support, oxygen saturation level was 82%. Since the case did not have fever and WBC count was as 8300/mm3, no infection was suspected. The laboratory findings revealed hemoglobin level as 13.4g/dL, glycosylated hemoglobin as 8.5, CRP > 32mg/L, albumin as 2.7g/dL and protein in urine as 3+. Since there was no finding of hemoptysis or anemia, alveolar hemorrhage diagnosis was not suspected. No coronary failure was detected in the cardiology scan performed in the cardiology clinic. Fiberoptic bronchoscopy did not reveal any finding of infection, inflammation or malignancy. The right lung was lavaged with 30mL of isotonic saline solution, which showed intensive infiltrative lesions in chest CT. The lavage specimen was in milky appearance. He reported that his complaints was relieved following bronchoscopy. However, due to a decrease in the oxygen saturation to 65% in the following hours, CPAP support using a mask is administered.

On the 2nd day of his hospitalization, pathological examination of the lavage specimen revealed that it is PAS stain positive. He was diagnosed as pulmonary alveolar proteinosis (PAP) and a whole lung lavage was planned. An informed consent was obtained. A positive end expiratory pressure was performed for the following three days, however, the oxygen saturation did not increase and he was supported by mechanical ventilation on CPAP mode. Same day he was intubated and underwent an urgent lung lavage. Following a double lumen selective intubation, 200mL serum physiological with approximately 36 °C was poured into the right lung. During the aspiration of the fluid, a sudden cardiac arrest occurred and resulted in mortality despite resuscitative maneuvers.

Discussion

Pulmonary alveolar proteinosis is a rare disease characterized by progressive accumulation of surfactant, phospholipid and proteins in alveoli and terminal airways leading to impairment of gas exchange. It occurs in three forms including idiopathic (primary), secondary and congenital [4]. Among the causes of secondary form are exposure to heavy inorganic dusts such as silica, titanium, aluminum, hematological and oncological diseases such as leukemia and lymphoma and etiological factors such as HIV and Pneumocystis carinii [5].

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PAP usually affects adults aged 20-50 years. It is a rare disease which could be asymptomatic and which could result in mortality. The most common complaints are cough and dyspnea. Other symptoms include fatigue, weight loss, fever, pleuritic chest pain and hemoptysis. Initial complaints of our case were progressive dyspnea and cough.

Characteristic radiological findings of PAP include nodular infiltration with a tendency to merge and ground glass density, septal thickening and resemblance to paving stone [6]. Similar findings can be found in hypersensitivity pneumonia, lung edema, alveolar hemorrhage, radiation pneumonia and sarcoidosis [7]. According to the literature, PAP predominantly affects upper and lower parts of lungs and peripheral lung remain protected (8). However, in our case lesions were also intensive in the periphery.

In cases of PAP, respiratory function tests reveal restrictive respiratory function disorder and mid-level decrease in CO diffusion test [9]. In our case, respiratory function test could not be performed because of advanced dyspnea. However, arterial blood gas analysis showed hypoxemia and increase in shunt fraction.

In cases of PAP, BAL fluid typically has a white-opaque appearance. Analysis of the fluid reveals inflammatory cell, alveolar macrophage, extracellular eosinophils materials and PAS positive material abundant in lipid and protein [6,8,10]. The pathological findings in our differential diagnosis were ruled out with anamnesis and examination. The diagnosis was made based on the typical appearance of lavage fluid and cytological examination of the fluid as PAS positive.

PAP treatment is often decided according to the progression of the disease, presence of infections and general clinical condition of the patient. 20% of the PAP cases can recover spontaneously and mortality in primary form is below 10% [9,11]. In cases with solitary lung opacities, resolution could develop from 3 to 9 months [12]. The aim of the treatment in PAP cases is to restore the alveolar gas exchange by removing excess surfactant accumulated in the alveoli. Despite studies on other treatment methods including systemic steroids, proteinosis, mucolytics, the standard accepted treatment method is still whole lung lavage. In a study conducted with PAP cases, symptoms were alleviated and radiological findings improved in the 52% of the 51 cases that underwent lavage and 94% of the 17 cases that were followed up [13]. There are reports arguing that approximately one third of the cases spontaneously recovered. However, it is also reported that pulmonary fibrosis developed in approximately one third of the cases despite repeating whole lung lavage [6]. The main treatment criteria include PaO2 < 65 mmHg, P (A-a) O2 > 40 mmHg, shunt fraction > 12%, and dyspnea with minimal effort [9].

Our case's treatment failure depends on its diagnoses was done at the end stage. Desaturation, cyanosis and intercostal retractions at arrival were indicators of bad diagnosis. Identification processes such as laboratory investigations and invasive procedures fulfilled at first day, pursuit of pathology obtained on the second day, and it was planned to wash lung on the third day. The day when the lung lavage was planned, the patient was desaturated and ventilated on CPAP mode by mechanical ventilator for three hours and because hypoxemia persisted the patient had intubated electively. After intubation, lung lavage had completed. Intubation had performed selectively with double lumen tube accompanied by bronchoscopy. In process, 200mL 0.9% NaCl was given and aspirated, so no fluid remained in the lung. We do not think that arrest depend on neither fluid nor process time.

Lung lavage for the treatment of PAP was first proposed by Ramirez-Rivera in the 1960's [14]. Nowadays lavage treatment is conducted under general anesthesia with approximately 60L serum physiological and using lung ventilation via double lumen endotracheal tube [12].

It announced that PAP patients who have bad general status, need of ventilation, have good results with extracorporeal membrane oxygenation (ECMO) support lung lavage [15]. However, our center has not ECMO background so we could not support the patient with ECMO. Because of the patient's instability, the patient could not transferred any other center. The deteriorated arrival of the patient to the hospital, fast progressive behavior of the disease, such cases has a high mortality risk. Although the complaints of our case started five months before and progressively increased, no diagno-

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sis could be done. This might have been because of the rarity of PAP cases and radiological findings showing similarities with other lung diseases.

As a conclusion, two characteristics of our case make it different from other reported cases. First of all, it did not present in age 20-50 years and secondly lung periphery has been affected as much as other parts of the lung. As a take home message we want to emphasize that PAP, which is seen in young adult age group, could be seen in older ages and radiological patterns could show differences.

Declaration of conflicting interests

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Case Report

A descending necrotizing mediastinitis case treated with early surgical intervention

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ABSTRACT

Descending necrotizing mediastinitis (DNM) can be described as a rare but severe infection that can develop after primary pharyngeal or odontogenic infections. The most important factor affecting the morbidity and mortality in DNM is early diagnosis and prompt treatment with early aggressive surgical drainage. Herein, we present a case of mediastinitis that developed after deep cervical infection that was treated with early surgical intervention, changing the course of the disease.

Keywords: mediastinitis, surgery, infection

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Introduction

Descending necrotizing mediastinitis (DNM) can be described as a rare but severe infection that can develop after primary pharyngeal or odontogenic infections. The mortality rate has not changed much today since the first case series of DNM which was reported in 1938 [1]. Currently, the mortality rate of the DNM varies between 14% and 50% despite modern treatment methods [2]. Herein, we present a case of mediastinitis that developed after deep cervical infection that was treated with early surgical intervention, changing the course of the disease.

Case Report

An 80-year-old male patient admitted to our emergency room (ER) with the chief complaint of difficulty in swallowing which started two months ago. Globus sensation in the throat, which started 20 days ago, right earache, sore throat and fever with the duration of 10 days accompanied the complaints. Patient's past medical history revealed that he was an ex-smoker with a history of 40 packages/day and quitted smoking 20 years ago. He was also diagnosed with COPD, but he was using his COPD drugs irregularly. His physical examination in the ER revealed a blood pressure of 130/92 mmHg, heart rate of 90/min, and fever of 38.6°C. Additional examinations revealed that his oropharynx was minimally hyperemic and right cervical region was erythematous and painful with palpation. His blood workup revealed a white blood cell count of 26,200/mm3 (N: 4500-10300/mm3) with 92.5% neutrophil, C-reactive protein of 33 mg/dL (N: 0-0,5 mg/dL) and an erythrocyte sedimentation rate of 45 mm/hr (N: 0-20 mm/hr).

The case was consulted with otorhinolaryngology (ORL) clinics with the pre-diagnosis of deep cervical infection. His cervical thoracic computerized tomography (CT) revealed an abscess formation in the retrotracheal space and he was hospitalized to the ORL clinics with the diagnosis of deep cervical infection. Emergency abscess drainage was performed through oral cavity under general anesthesia at the same day by ORL clinics. Methicillin resistant Staphylococcus epidermidis (MRSE) was found in the culture results of the abscess material and the case was consulted with the infectious diseases clinics. An antibiotherapy consisting Vancomycine 4x500 mg IV, Imipenem 4x500 mg IV and Metronidazole 2x500 mg IV was administered. He was consulted with our clinics at the 4th post-operative day because of ongoing fever and leukocytosis. His physical examination revealed tenderness in the cervical region on palpation. His lung auscultation was normal. Thorax CT revealed mediastinal air fluid levels compatible with DNM, starting from cervical region down to the sub-carinal space especially on the right side of mediastinum (Figure 1).

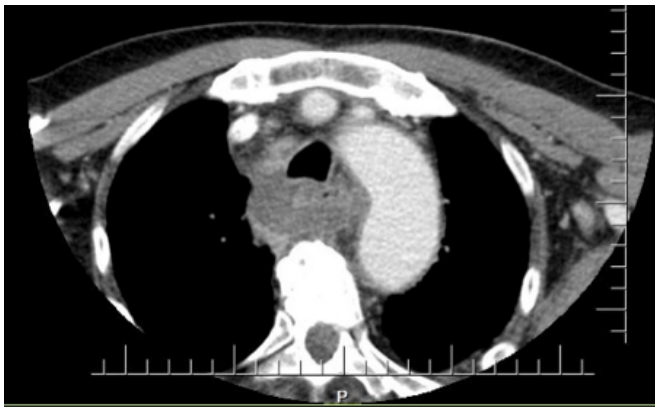

Figure 1. Thoracic computed tomography of the patient

Patient was transported to the operating theater immediately in order to perform an urgent mediastinal debridement with the pre diagnosis of DNM. General anesthesia was performed using a double lumen intubation tube. Videothoracoscopic exploration was performed through the right 5th intercostal space (ICS) via one 10.5 mm thoracoport. Pleural effusion was found and samples were obtained. However, patient's age and his irregularly treated COPD with infective status caused his blood oxygen saturation levels drop during surgery and patient did not tolerate single lung intubation. Thus, videothoracoscopy was converted to posterolateral thoracotomy through the 5th ICS. Serratus anterior muscle was spared during the procedure. Intraoperative exploration revealed an abscess formation at 4-5 cm superior to the azygo-caval junction protruding into the thoracic cavity just anterior to the esophagus (Figure 2).

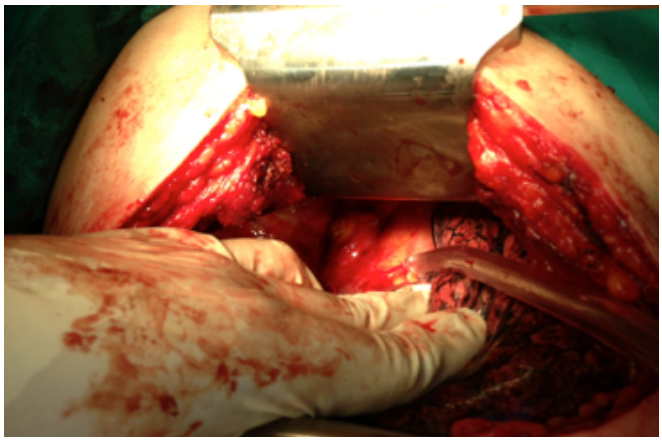

Figure 2. Intraoperative view of the mediastinum

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The yellowish white colored dense fluid content of the abscess was drained and samples were collected. The abscess cavity was further explored. The cavity reached up to 3-4 cm superiorly into the paravertebral space and 3-4 cm inferiorly until carina. These additional sites were thoroughly debrided as well. Patient was extubated in early postoperative period and was transferred to the intensive care unit (ICU). Mediastinal pus collection was evaluated with daily intravenous contrast enhanced thorax CT. The leukocyte count on the first postoperative day was 14,900/mm3. Patient was transferred to our clinic at the postoperative second day as his general condition improved, and there were no additional mediastinal collection or air-fluid levels on thorax CT. Chest tubes were removed (apical on the 5th, basal on the 7th postoperative day) as the drainage from the chest tubes decreased and the color of the drained fluid became serous. The fever also resolved. The microbiological culture results of the pleural effusion and abscess material obtained during surgery revealed no bacteria attributable to the broad-spectrum empirical antibiotherapy he was receiving. He was discharged on the 10th postoperative day as his physical examination revealed bilateral normal lung auscultation findings with normal posterior-anterior (PA) chest x-ray and blood tests revealed diminished leukocytosis. His outpatient clinics examination one week after he was discharged was normal. The thorax CT on postoperative third month revealed no abnormal findings in the mediastinum.

Discussion

DNM usually occurs following odontogenic infections [3]. DNM occurs as the deep cervical infection descends through the paratracheal, prevascular and retropharyngeal spaces and reaches the mediastinum. This descend is thought to be facilitated by gravity, respiration, intrathoracic negative pressure and the destructive effects of the enzymes of the bacteria involved [4]. We identified that our case had DNM secondary to a deep cervical infection started at retropharyngeal space as well. However, our patient did not have any predisposing factor for the development of the deep cervical infection such as dental procedures, oropharyngeal trauma, epiglottitis, cervical trauma, cervical lymphadenitis or endotracheal intubation. The identification of deep cervical infection in our patient was a strong risk factor by itself for the development of DNM and thus together with the clinical findings compatible with mediastinitis we could establish the DNM diagnosis.

DNM is treatable with a broad-spectrum antibacterial treatment and early surgical drainage. The etiological microorganisms that are isolated in DNM patients usually consist of Streptococcus, Bacteroides, Staphylococcus, Peptostreptococcus, Fusobacterium, Propionibacterium, Stenotrophomonas, Pseudomonas species that are aerobic and anaerobic bacteria and fungi of Candida species [5]. Multiple microorganisms were reported to be isolated in 29% of the DNM patients [6]. We isolated MRSE in our case. The culture and antimicrobial susceptibility tests for the MRSE revealed that the isolated bacteria was susceptible to Vancomycine but in order to achieve a broader spectrum for any additional microorganisms that could not be identified we continued administering Imipenem and Metronidazole to the patient.

It was also reported that especially immunodeficiency secondary to diabetes mellitus (DM) is an important risk factor in the development of DNM [7]. We believe that the absence of DM in our case contributed to the good prognosis.

In addition to these, the most important prognostic factors in DNM were advocated as early diagnosis and prompt treatment [8]. The most important factor in achieving early diagnosis in DNM is clinical suspicion. Clinical suspicion attributable to the long lasting sore throat and fever in our case helped us establishing the deep cervical infection. Early diagnosis and prompt surgical drainage of the cervical and mediastinal regions and early administration of broad-spectrum antibacterial treatment affected the patient's clinical status in a good way.

As conclusion, the most important factor affecting the morbidity and mortality in DNM is early diagnosis and prompt treatment with early aggressive surgical drainage. Broad-spectrum antimicrobial treatment tailored according to the culture results of abscess material will significantly improve the prognosis in DNM patients.

Declaration of conflicting interests

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Case Report

Surgical results of herpes zoster and lung cancer association in preoperative period

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ABSTRACT

Herpes zoster also known as shingles is a disease caused by the reactivation of varicella zoster virus. It often starts with erythema as the first finding. Maculopapular vesicles may form painful rashes with maturations, which may be painful at baseline before the onset of rash. Here, the postponement of the operation due to the central mass located in the left lobe of the patient due to herpes zoster, and the possible results were presented.

Keywords: herpes zoster, lung carcinoma, mediastinoscopy, pneumonectomy

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Introduction

Herpes zoster, commonly known as shingles, is a disease caused by the reactivation of varicella zoster virus (VZV). Herpes zoster is characterized by an unilateral vesicular rash accompanied by severe neuralgia. It is caused by the reactivation of the varicella zoster virus lying in the sleeping sensory ganglia following the primary infection. The risk of reactivation increases with age and it is estimated that herpes zoster develops in about 50% of the people living up to 85 years [1]. Here, a 76-year-old man who was scheduled for surgery due to squamous cell carcinoma where the surgery was delayed for 3 weeks due to herpes zoster diagnosed in the preoperative period is presented in the light of the relevant literature.

Case report

A 74-year-old male patient applied to our clinic with complaints of cough and back pain in the left region. His biography includes hypertension and active smoking. There is no obvious feature in the physical examination. Blood pressure was 135/90 mm/Hg, pulse was 100 beats/min, fever was 36.5 °C and respiratory rate was 24/min. In blood count white blood cell count was 6300/mm3 (68.3% neutrophil and 15% lymphocyte), erythrocyte sedimentation rate was 91 mm/hr, while other laboratory parameters were within normal limits. Posterior anterior (PA) chest X-ray showed increase in density in the left hilar region and in the left lower zone (Figure 1).

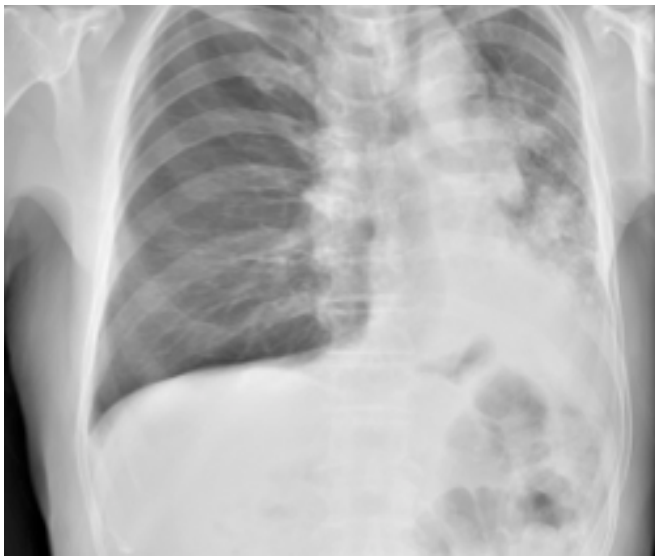

Figure 1. Posterior anterior (PA) chest X-ray shows increased density left ventricular density and lower left zone.

Chest computed tomography (CT) and positron emission tomography (PET/CT) reported a 50 mm central mass (SUVmax: 13) in the left upper lobe of the lung (Figure 2).

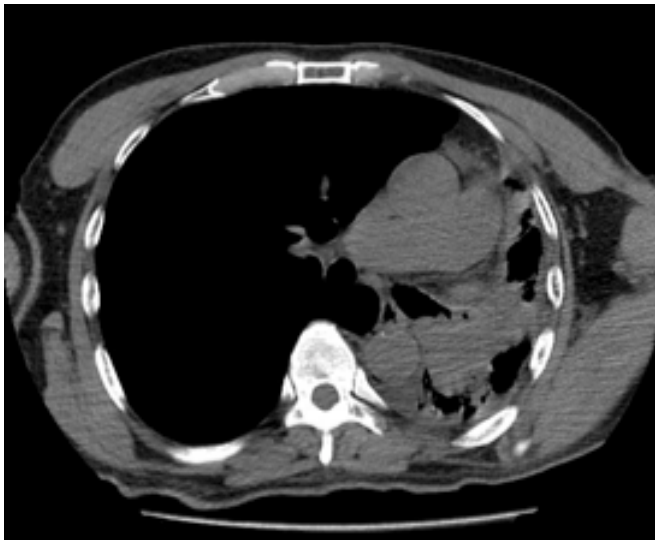

Figure 2. Chest computed tomography revealed a 50 mm central mass in the upper lobe of the left lung.

Fiberoptic bronchoscopy (FOB) examination revealed an endobronchial lesion in the left upper lobe bronchus and biopsy was reported as squamous cell carcinoma. Lung function tests were within normal limits (FEV1: 2.1 L). The patient was found to have suspicious mucocutaneous lesions (Figure 3) and no pathology was detected in the biopsy of these lesions. Herpes zoster was diagnosed clinically.

Figure 3. Neck and especially left-sided weighted rash, peripheral erythematous, small, round and diffuse vesicles.

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Analgesic and acyclovir treatment lasted for fourteen days. Common erythema after two weeks of VZV treatment is seen in Figure 4.

Figure 4. Common erythema after two weeks of VZV treatment.

Mediastinoscopy was performed and lymph nodes (2R-4R-7) were primarily sampled. Left pneumonectomy was performed with thoracotomy on preoperative lymph node reactive residence. The case was pathologically staged as T3N0M0 Stage IIB. The patient was discharged uneventfully with no recurrences at 18 month follow-up.

Discussion

Herpes zoster is a contagious disease caused by the reactivation of varicella zoster virus. The virus is often dormant in sensory ganglia of cranial and spinal nerves after chickenpox, but may resume in patients due to advanced age, immunosuppressive medical conditions and malignancies [1]. Epidemiological studies have shown that zoster events have increased in recent years. It is estimated that between 10% and 20% of the world population will suffer life-threatening zoster. There are about 60,000 to 300,000 cases annually in the United States and the majority of this patients are over 50 years old [2]. Risk factors that may increase the likelihood of shingles include immunosuppression, advanced age, some neoplasms and systemic diseases. The reasons behind the reactivation of the VZV are not clear [3]. Lung cancer and VZV findings were detected at the same time in our case of 76 years old.

Herpes zoster can usually be diagnosed clinically. However, the diagnosis can be confirmed by the vesicle exacerbations seen with the viral cultures of the vesicular juice, which reveal the multicellular giant cells. Histology reveals inflammation and neuronal loss in the corresponding ganglia in affected dermatomes [4]. In our case, lung cancer and VZV were detected in the same hemithorax region. It shows that VZV may be a secret cancer marker. Evidence for subtype cancers suggests a strong association between herpes zoster and occult hematological cancer. In an anthropological review published in 1995, the relationship between herpes zoster and the diagnosis of subsequent malignancies was examined. Based on only two small basic publications of this review, the authors of the review concluded that there was no increased risk of cancer within herpes zoster patients [5]. Various biological mechanisms explaining the relationship between cancer and herpes zoster has been previously suggested [6]. Findings of VZV in our patient may be related to lung cancer. First, carcinogenesis can induce immunodeficiency, which causes the herpes zoster to burst in the preclinical asymptomatic stage. In particular, it may lead to impaired number and function of B-cells and T-cells positively associated with hematological cancers and these cancers. The risk of hematological cancer increases even 5 to 10 years after the herpes zoster and this immunosuppressive effect indicates that diagnosis of cancer can be detected several years ago [7]. Cellular immune function is firstly important for suppressing varicella-zoster virus replication. Secondly, cellular immune function is crucial to suppress varicella-zoster virus replication and carcinogenesis. For this reason, herpes zoster may be a marker of impaired immune surveillance in the host and in this case causes cancer development. For example, immunosuppression in autoimmune diseases can increase the risk of herpes zoster and some cancers [8]. Thirdly, it is possible that recurrent antigenic stimulation resulting from subclinical and eventual activation of the clinical varicella zoster virus leads to exacerbation of precancerous genetic lesions or triggering neoplastic transformation. Various herpesviruses act directly on tumor-induced disease through inflammation, decreased immunity and immunosuppression. A direct carcinogenic effect of herpes zoster may also explain the cancer development in previous areas affected by herpes zoster [9].

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Shingles can occur with local trauma or procedures. The majority of the reported cases develop in the same dermatome as the previous trauma. However, several cases have been reported about where the rashes are located in the real incision area. These cases show that shingles events developed around an incision site may mimic other rash causes. There were very few reports on the surgical incisions of the patients that developed shingles. While Godfrey et al reported that the thoracic surgeon for scoliosis was a zona-developing disease at the surgical incision site, Choi et al published a case report of a patient who developed a herpes zoster within the last face surgery scar [10]. Thomas et al. published a case-control study showing that the risk of shingles increased for one month following trauma, 39 studies in this study identified an increased risk for breast cancer during the next two years of radiotherapy [11]. However, Gadient et al. studied the time interval between the process and the development of the rash [12]. The purpose of treating shingles is to reduce the duration of symptoms of the disease, reduce the risk of transmission and prevent post-herpetic neuralgia. Post-herpetic neuralgia is a syndrome that develops in about 10% to 15% of cutaneous hypersensitivity and neuropathic pain and is particularly difficult to treat [13]. Our case was operated after VZV treatment.

Only a few studies have examined the interactions with age and time after the diagnosis of malignancy [14]. As a conclusion, the relationship between herpes zoster and malignancies should be kept in mind.

Declaration of conflicting interests

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Case Report

Inflammatory myofibroblastic tumor: a case of a rare tumor of lung

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ABSTRACT

Inflammatory myofibroblastic tumor (IMT) is a rare thoracic lesion, the diagnosis of which should be supported by histological and immunochemical examinations. Although this is known as a benign tumor, it should be completely resected, and patients should be closely monitored to avoid any local invasion or recurrence. This article presents a 34-year-old female patient who has endobronchial polypoid IMT that is rarely seen among IMT patients. Inferior lobectomy and lymph node sampling was performed. The patient had no local recurrence and metastasis free at the end of first year postoperatively and follow-up is ongoing.

Keywords: inflammatory myofibroblastic tumor, solitary fibrous tumor, lung cancer

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Introduction

Inflammatory myofibroblastic tumor (IMT) is uncommon among primary lung cancers. It constitutes 0.04% to 1.2% of all lung tumors, and may occur at any age group [1]. The aim of this case report is to identify the clinical approach to this rare tumor and highlight the key features with a review of the relevant literature.

Case Report

A 34-year old female presented with the complaint of a dry cough that had been ongoing for one month. On the pulmonary radiographs, a mass lesion was determined in the left inferior lobe.

On the thoracic CT image, a mass lesion of 46 x 42 mm was observed with spicular extension and showing lobulation at the left inferior lobe in close proximity to the inferior pulmonary vein. On the PET-CT SUVmax value of the mass in the left inferior lobe was 20.6 and no other pathological involvement was determined. The histopathological examination of bronchoscopic biopsy reported spindle cell proliferation and inflammatory granulation tissue (Figure 1).

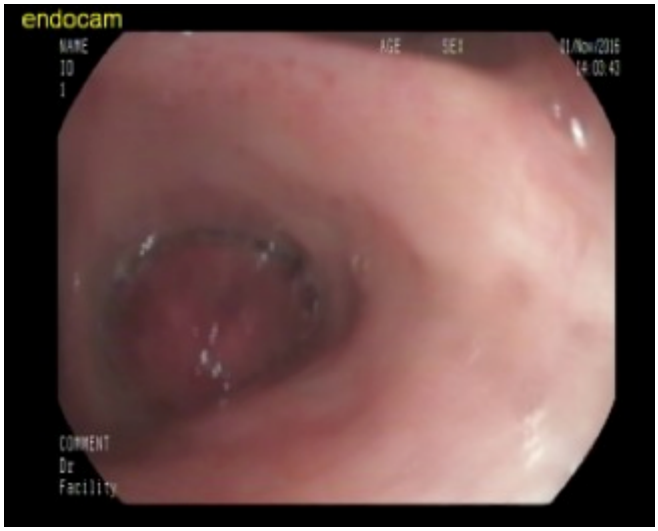

Figure 1. Fibreoptic bronchoscopy image of the polypoid lesion in the left inferior lobe bronchus.

Due to the close proximity to the inferior pulmonary vein, a thoracic MR was performed, demonstrating a mass lesion with a wide base on the pleura, showing calcifications. A fibrotic component showing heterogeneous contrast involvement was seen after the administration of intravenous contrast material (Figure 2). Cranial metastasis was ruled out by cranial MR.

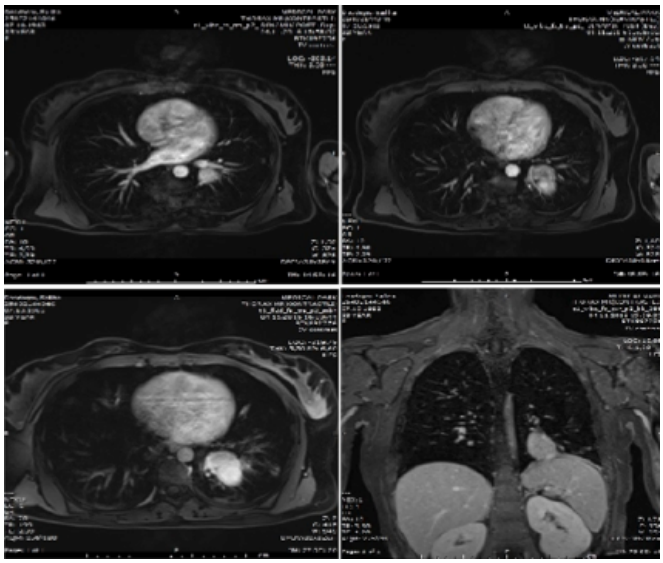

Figure 2. Thoracic MR showing a mass lesion with a wide base on the pleura and having calcifications. Also including a fibrotic component with heterogeneous contrast involvement. Hypointensity was determined on T1-weighted images and hyperintensity on T2 images.

A left lateral thoracotomy was performed and a biopsy was taken from the mass. The frozen section was reported as mesenchymal tumor than a lower lobectomy and lymph node sampling was performed.

The histopathologic examination reported a mesenchymal tumor in the bronchial lumen invading the bronchi and parenchyma. Tumor cells were in the form of bundles with spindle, hyperchromatic nucleus and cytoplasm with undefined borders and scattered lymphoid cells. SMA was focal positive, S-100 and CD34 was negative. The pathological diagnosis of the lesion was inflammatory myofibroblastic tumor. The surgical margins were tumor free and lymph nodes showed no metastasis.

The patient was discharged on postoperative day 5 uneventfully. At the 12-month postoperative follow-up examination, no recurrence or metastatic findings were found.

Discussion

Inflammatory myofibroblastic tumor was first reported in the lungs by Brunn in 1939 [2]. It was first named by Umiker et al. in 1954 due to the tendency to mimic a malignant process both clinically and radiologically [3]. Due to the variable cellular components, various terms

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have been used to describe IMT, including plasma cell granuloma, inflammatory pseudotumor, xanthogranuloma, inflammatory fibrosarcoma and pseudosarcomatous myofibroblastic proliferation [1]. In 2002, the World Health Organization classified IMT as an "intermediate malignancy (rarely metastasizing)" [4]. However, a recent study of chromosomal translocation involving ALK gene stated that it was present in 50% of IMTs, thereby suggesting that approximately 50% of IMTs could be malignant [5].

IMT can develop in any age group and both genders are affected equally where the lungs and abdomen are the most commonly affected locations [5,6]. The typical location is in the lung parenchyma, but also it has been reported in the trachea or the bronchi [1,7].

Preoperative diagnosis of pulmonary IMT is difficult due to the diversity of radiological manifestations [6]. Although endobronchial polypoid forms developing in the bronchus are the most uncommon form, there have been reported cases, and chest radiography only reveals non-specific finding such as pulmonary atelectasis or obstructive pneumonia [8]. Kim et al, reported that the most common radiological presentation was a solitary, peripheral, well-circumscribed lung mass [9]. On MR imaging, the mass is typically isointense to muscle on T1-weighted images and hypo- to hyperintense on T2-weighted images, depending on the fibrous contents. Heterogeneous contrast enhancement is seen on post-contrast MR images with delayed persistent enhancement [8]. On PET scans, positive FDG uptake similar to that of a malignant tumor can be seen [1].

In the histopathological analysis, IMT can be seen to be composed of spindled myofibroblasts, fibroblasts, and inflammatory cells (lymphocytes, plasma cells, and eosinophils). It has been reported that approximately 60% of IMT cases have a rearrangement of the ALK gene on chromosome 2p23, which has been suggested as responsible for tumor transformation [5]. In immunohistochemical examinations, tumor cells show strong diffuse positivity with smooth muscle actin and vimentin, and are negative for cytokeratin, CD34 and S100. In the current case, the diagnosis of tumor was made from the general appearance and the determination of S-100 (-), and CD34 (-) [6].

There have been very few reports of multiple metastasis of IMT, and local recurrence has been reported as 6.6%-13% following incomplete resection [4,10]. For pa¬tients undergoing complete resection of IMT in the lungs, prognosis is known to be favorable with survival rates of 91% at 5 years and 77% at 10 years [10]. Of the anticancer drugs available, in some cases in which ALK is positive on immunohistochemisty staining, crizotinib, an ALK inhibitor, may be effective [7]. In the current case, this was seen with pathological examination postoperative to complete resection and no additional treatment was applied.

Declaration of conflicting interests

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Case Report

Pulmonary congenital cystic adenomatoid malformation accompanied with hamartoma in an adult: report of a case

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ABSTRACT

Congenital cystic adenomatoid malformation (CCAM) is mostly recognized in children and adult presentation is rare. Here, a 42-year-old male patient was presented. He had a previous history of pneumothorax, and radiologically there were multiple bullous lesions in the right upper lobe, as well as a nodular lesion of 2 cm. He underwent right upper lobectomy and middle lobe wedge resection which revealed CCAM type I and hamartoma of the lung. Less than 70 adult cases of CCAM have been reported in the literature. Lung cancer accompanying CCAM or malignant transformation in adult are rarely described. But to our knowledge, this is the first adult case of CCAM with hamartoma. CCAM should be considered in the differential diagnosis of multicycstic lesions in adults with a history of pneumothorax, and the surgical resection is the treatment of choice.

Keywords: hamartoma, lobectomy, cystic adenomatoid malformation of lung

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Introduction

Congenital cystic adenomatoid malformation (CCAM) of the lungs are rare congenital cystic lesions with an incidence of 1 in 25,000 to 35,000 pregnancies [1]. CCAM is firstly defined as a distinct disease by Chin and Tang in 1949 [2]. The disease was classified into 3 groups, then expanded into 5 types with a new name as congenital pulmonary airway malformation [3,4]. Most cases (80 to 85%) are recognized in the first 2 years of life, and adult presentation of CCAM is uncommon [5,6]. CCAM in adults may be complicated by pulmonary bacterial infections and accompanied by adenocarcinoma of the lung [5-7]. Here we described an adult CCAM case accompanied by hamartoma and treated with lobectomy.

Case Report

A 42-year-old non-smoker male patient presented with progressing dyspnea and dry cough. Dyspnea was mostly seen on exertion, and the patient reported that this affected his work and quality of life during the last two years. He had a history of a right pneumothorax treated with chest tube 19 years ago. On admission, the patient had normal vital signs, no fever. The laboratory test results did not show any abnormalities. Pulmonary and cardiac physical examination were unremarkable. Chest X-ray showed increased hyperlucency in the right upper zone. High resolution computed tomography (CT) of the chest demonstrated multiple bullous lesions of several diameters (2 to 7 cm), and a nodular lesion seized 2.0 x 1.4 cm in the right upper lobe (Figures 1a-c). PET-CT scan revealed a SUVmax value of 0.4 for the nodular lesion. Bronchoscopy was negative for any bronchial lesions. Since the patient had a previous history of pneumothorax, and multiple bullous lesions accompanied by a nodule of unknown pathology, a surgical resection was planned. The patient underwent a right upper lobectomy and middle lobe wedge resection without complication via a right posterolateral thoracotomy, since the videothoracoscopic approach was found unsuitable due to dense and heavy adhesions. The patient developed prolonged air leak and discharged with a Heimlich valve on the in the postoperative 9th day. The air leak dissolved and the valve was removed on the 14th postoperative day. The patient had an uneventful follow-up of 10 months without further complaints. He reported that the dyspnea resolved and he could return to his normal daily activities.

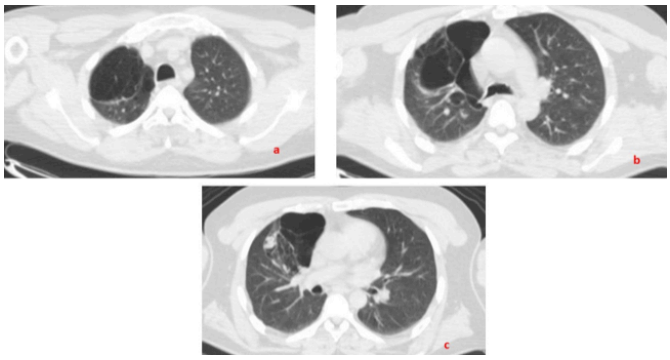

Figure 1a-b. Chest computed tomography of the patient demonstrating multiple cystic lesions seized 2 to 7 cm located at the right upper lobe, **c.** nodular lesion in the same lobe.

The pathological examination of bullous right upper lobe revealed multiple cystic lesions with adenomatous changes. Most cysts were lined by ciliated and some by pseudostratified columnar epithelium. The stroma around the cysts was mostly infiltrated by lymphocytes, and nearby capillaries were dilated which demonstrated chronic inflammation. There was no cartilage in the cyst walls (Figure 2a). These findings were consistent with type I CCAM. The pathological examination of the nodular lesion located nearby the bullous parts of the upper lobe demonstrated hyaline cartilage and foci of adipose tissue surrounded by cleft-like spaces lined by respiratory epithelium, indicating a pulmonary hamartoma (Figure 2b). There was no evidence of malignancy in the resected specimens.

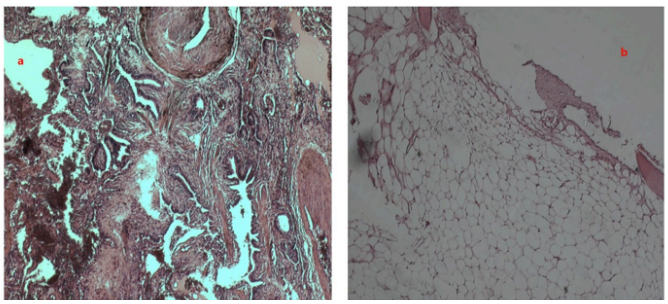

Figure 2a. Photomicrography of the lesions demonstrating multiple varying-sized cysts lined by ciliated and pseudostratified columnar epithelium without the presence of cartilage, **b.** foci of adipose tissue surrounded by respiratory epithelium, indicating a pulmonary hamartoma (HEx100).

Discussion

We reported an adult case with type I CCAM based on

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the radiological and pathological results. Type I CCAM is the commonest type corresponding to 65% of the cases. This type consists of one or multiple cysts measuring 3 to 7 cm and often affecting one lobe. The patient may be asymptomatic or have respiratory distress of several degrees. There are no other associated anomalies. Microscopically the cysts are lined with ciliated columnar epithelium. Mucigenic adenomatous cells are common. The presence of cartilage is extremely rare. Type II CCAM is formed by multiple middle-sized cysts (0.5 to 2 cm) and its incidence is 10 to 15%. Most cases are associated with other anomalies, most of which are incompatible with life. This type has no mucosal cells or cartilage. Type III CCAM is rare (5%) and characterized by clumps of small cysts not exceeding 0.2 cm. This type may involve the whole lung [3]. In 2002, two other types of CCAM were described [4]. Type 0 CCAM has firm and small lungs, and shows bronchiolar type airway with cartilage, smooth muscle and glands. Finally, type IV CCAM has peripheral large cysts of more than 10 cm lined by flattened epithelium.

Eighty to 85% of the cases are recognized in the neonatal period, however there are several reports in adults [8,9]. Besides there exist three studies as review of the literature consisting of 11 to 60 patients [5-7]. Overall, less than 70 cases of adult cases with CCAM have been reported. Type I CCAM is more common in adults. Type II CCAM is reported in 17 to 45% [5-7]. The only patients with type III CCAM was reported by Barreiro et al [5]. According to these limited number of patients, CCAM in adults is seen in patient aged between 20 to 80 years, with a slight male predominance, and mostly involves upper lobes. Our patient has 42 years-old and the disease affected mostly right upper lobe and some part of the middle lobe.

In adult patients, CCAM may cause pneumonia, abscess formation, fungal and tuberculous infections, hemoptysis, and air embolism [8]. A history of pneumothorax has been reported in only 8 patients [6,7,9]. As far as we know, our patient has the 9th adult case with previous pneumothorax.

The presences of either accompanying lung cancer or malignant transformation are rare but troublesome problems in adult patient with CCAM. Hamanaka et al [8] reported 8 patient with adenocarcinoma in their review consisting of 60 patients. Pulmonary tumorlets have been reported only once [10]. To our knowledge, our patient is the first case of CCAM accompanied with hamartoma.

The treatment of CCAM in adults, as well as in children, is the complete surgical resection. Lobectomy is the mostly preferred resection type, followed by segmentectomy, pneumonectomy, and wedge resection [5-8]. We performed a right upper lobectomy and middle lobe wedge resection to achieve the complete resection.

In conclusion, CCAM should be considered in the differential diagnosis of multicycstic lesions located in one lobe in adults with a history of pneumothorax, although adult cases of CCAM are very rare. The surgical resection is the treatment of choice in all cases of CCAM to perform a histological examination of the lesion and to prevent potential neoplastic transformation.

Declaration of conflicting interests

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Case Report

Rapidly growing chest wall tumor of a pregnant woman: Ewing's sarcoma

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ABSTRACT

The incidence of coexistence of pregnancy and malignancy is approximately 1 in 1000-3000. Soft tissue sarcomas compose a very little portion of malignancies and Ewing's sarcoma is one of these tumors, which is very rare, and the most lethal of all. We report a 37-year-old female at gestational age of 23 weeks with a rapidly growing tumor on the right chest wall and managed with chest wall resection and reconstruction. The togetherness of pregnancy and Ewing's sarcoma is a rare entity and there is no exact information for treatment in the literature except a few case reports.

Keywords: Ewing's sarcoma, pregnancy, chest wall

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Introduction

The incidence of coexistence of pregnancy and malignancy is approximately 1 in 1000-3000. Soft tissue sarcomas compose a very little portion of malignancies, and 137 cases were reported between the years of 1963-2016 and only 19 of these were Ewing's sarcoma (ES) [1]. ES is one of these tumors, which is very rare, and the most lethal of all [2]. We present a case of ES underwent chest wall resection and reconstruction because of rapidly progressing mass on the chest wall by the onset of pregnancy.

Case Report

A 37 year-old female at a gestational age of 23 weeks (gravida: 2, para: 1) admitted with the complaints of pain and swelling on the right lower region of chest wall. Approximately a 6 cm diameter mass-like lesion was palpated on the lower region of right hemithorax. Laboratory findings were normal and β-hCG level was compliant with gestational age. A 70 x 35 mm diameter, heterogeneous mass with cystic components, elongating to intercostal area was detected in ultrasonography (USG). Magnetic resonance imaging (MRI) revealed a 75 x 44 mm mass invading sixth rib and causing irregularity on the contours of liver by compression with hyperintensity in T2A and iso-hypointensity in T1A sections (Figure 1). The patient was consulted with gynecology and obstetrics clinic, in consequence of obstetric USG showing compliant fetal findings with the gestational week, they mentioned the patient could be operated with close fetal monitoring.

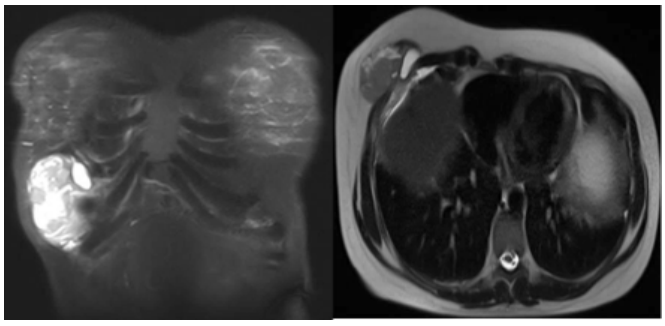

Figure 1. MR images of tumor in T2A and T1A sections.

En-bloc resection of the mass with the invaded sixth rib and reconstruction by prolene mesh was performed. The postoperative course was uneventful. The patient was discharged on fourth day after the removal of thorax drain on third day. Histopathological examination reported an 8 cm diameter round cell sarcoma with bone invasion, immunohistochemical findings support Ewing's sarcoma, resection margins were tumor-free (Figure 2).

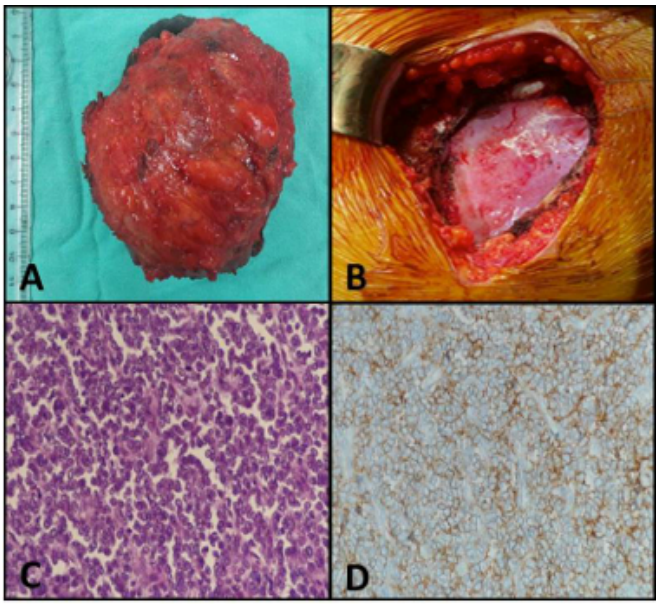

Figure 2A. Macroscopic sight of resected tumor with adjacent tissues, **B.** Reconstructed chest wall defect with prolene mesh, **C.** The tumor composed of round cells (Haematoxylin and Eosin x400), **D.** Immunohistochemically membranous CD99 positivity of tumor cells (x200).

After histopathological diagnosis, the patient was followed up until the termination of pregnancy with a healthy newborn at the gestational age of 35 weeks. The oncologists planned adjuvant chemotherapy after evaluation with positron emission tomography. The patient is under follow up for nine months without any recurrence.

Discussion

Ewing's sarcoma is a member of tumor family including peripheral primitive neuroectodermal tumors and Askin tumors [1]. Primary lesion is most commonly localized in femur, pelvic bones, humerus, fibula, clavicula or tibia, localization in rib, scapula and vertebrae is very rare. The rib localization has better prognosis. Initial findings are pain and tenderness by the growth of tumor [1,2].

Multimodal therapies like chemotherapy, radiotherapy, surgery and combinations form the treatment of ES [3]. The main treatment include chemotherapy and

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surgical resection if possible. Treatment with radiation alone has declined in the past 30 years because of secondary malignancies due to radiotherapy, though it is a radio-sensitive tumor. The survival of patients whose primary tumor were resected is reported to be longer than the patients treated with chemo-radiotherapy [4].

Decision of mother and family is important for the type and time of the treatment. Chemotherapy can be planned according to the gestational age or it can be postponed after the termination of the pregnancy. In literature, successful treatment of ES by chemotherapy without any complication were reported but cases with fetal mortality secondary to chemotherapy were reported also [5].

The number of cases in literature is not enough for an exact decision for treatment. This is the first case, which underwent chest wall resection for ES during pregnancy. Surgical treatment was provided without any complication and gained time for chemotherapy, which might have serious side effects on fetus. Preoperative biopsy was not planned because of the tumor characteristics and to avoid tumor seeding if malignant. As a conclusion, resection should be offered for the treatment of ES in selected patients after the decision of family and other disciplines.

Declaration of conflicting interests

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Case Report

Primary malignant mediastinal germ cell tumor in childhood

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ABSTRACT

Primary malignant mediastinal germ cell tumors are rare in childhood. Despite the metastasis to lung, liver, brain and bone is possible but sternal metastasis is unusual. Both tumor and its metastases treated with surgical resection, if possible followed by chemotherapy. We present a case primary malignant germ cell tumor, which has metastasis to lung and to sternum. We performed complete tumor resection, metastasectomy, sternal resection and then reconstructed by titanium plate and polypropylene graft.

Keywords: chest wall tumor, germ cell tumor, reconstruction of sternum

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Introduction

Mediastinal germ cell tumors (GCTs) are rare in childhood. Primary malignant mediastinal GCT (PMMGCT) is exceedingly rare and representing 0.32-2% of all childhood cancers [1]. They can metastasize to lung, liver, bone and brain but sternal metastasis is unusual [2]. They treatment is with multidisciplinary approach that includes surgery, chemotherapy (CT) with or without radiotherapy (RT) [1].

We present a case primary malignant germ cell tumor, which has metastasis to lung and sternum. After resection of the sternum totally, a sternal reconstruction with a tough prosthesis should be performed to protect intrathoracic organs from injuries and infection which will also help to prevent the paradoxical respiration. Recently, polypropylene mesh with moldable titanium plates and costal clips combination were used in chest wall reconstruction [3]. According to our knowledge, there was no report in the English literature about a PMMGHT case which metastasized to sternum and due reconstructed by polypropylene mesh with titanium plates and costal clips after a total sternal resection. Here, we intent to present this case and our clinical experience.

Case Report

A 13-years-old male who was suffering from persistent cough and chest pain for a month were examined in pediatric clinic. The posteroanterior chest x-ray showed a mediastinal enlargement and lateral x-ray revealed an anterior mediastinal mass (Figure 1). Computed tomographic scan of the chest (CT) showed a 19 x 19 x 12 cm size mediastinal mass that placed in anterior mediastinum (Figure 2).

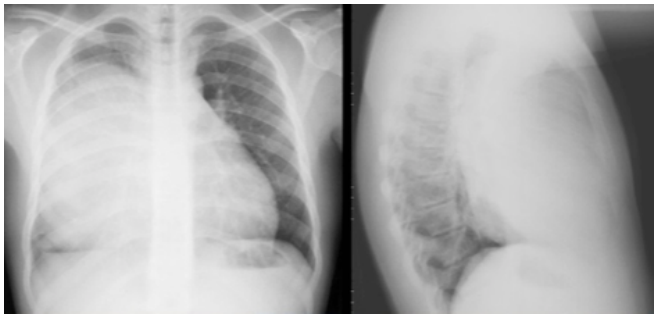

Figure 1. Mediastinal mass is shown in posteroanterior and lateral chest X-ray.

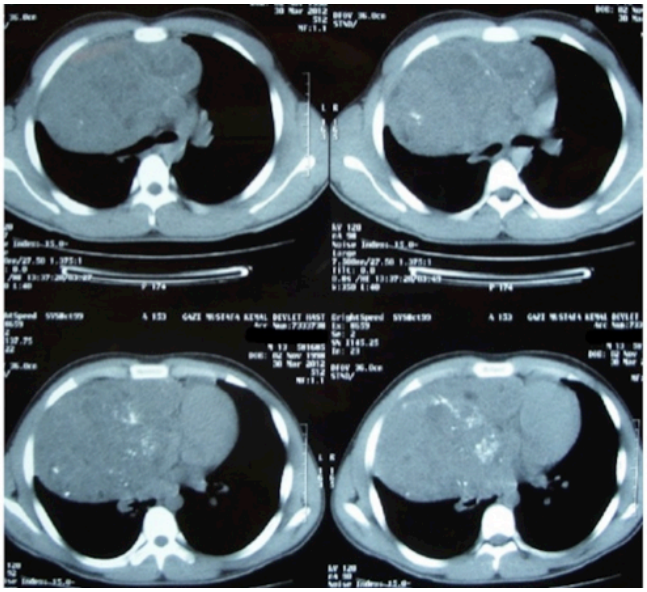

Figure 2. Chest CT shows the anterior mediastinal mass sized 19x19x12 cm at the right hemithorax.

Routine blood tests were normal except the liver function test that were higher at the border. The serum level of alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (b-HCG) of this patient were elevated. (AFP > 3000 ng/mL (normal range = 0-20 ng/mL) B-HCG=178.42 mIU/mL (normal range = 0-10 mIU/mL)). Carcinoembryonic antigen (CEA) level was 2.76 ng/mL which was slightly higher (normal range = 0-2.5 ng/mL). His scrotal ultrasonography and whole body bone scintigraphy were normal. The patient was referred to our clinic with the prediagnosis of mediastinal mass. While the patient was hospitalized, an informed consent was taken from his parents. After essential preoperative preparation, we performed biopsy from the mass by right anterior mediastinotomy as a small specimen via a needle biopsy might not be sufficient for an immunohistochemical study and which might lead to a dignostic confusion. Furthermore, heterogeneity of the tumor and areas of necrosis might decrease the reliability of a needle biopsy. Frozen section was reported as mature cystic teratoma. Whereat, in the same session, we performed right posterolateral thoracotomy. A capsuled mass that is filling almost all hemithorax was determined in the exploration and excised totally (Figure 3). Postoperative pathological result was reported as, mixed germ cell tumor that included immature and mature components (yolc-sac-tumor + choriocarcinoma + seminoma). The chemotherapy protocol that included gemcitabine, docetaxel and paclitaxel in pediatric on-

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cology clinic was started and the patient was followed periodically. The AFP values decreased to 13.4 ng/mL with the effect of chemotherapy.

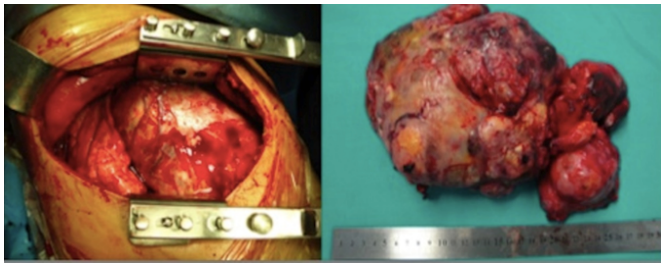

Figure 3. The image of the mass intraoperatively and macroscopic specimen.

After the third cure at postoperative eighth month, chest CT showed a 12 x 19 mm lobule nodule at the right lower lobe of the lung, a 12 mm nodule at adjacent the major fissure and 17 mm hypodense area at anterior mediastinum. AFP values were progressively increased and reached to a level of 13.309 ng/mL. Whereupon, mediastinal mass excision, multiple wedge resection and lymphatic node excision was performed by right rethoracotomy. Pathological results verified the mediastinal mass was a mixed germ cell tumor (yolc-sac-tumor + embryonal carcinoma), all wedge resections were yolc-sac-tumor metastasis and the number 11 lymph node was mature cystic teratoma metastasis. A 13-cure chemotherapy protocol that including Vincristine, Actinomycin-D, Cyclophosphamide and Adriamycin (VACA) was started. Again, AFP levels were declined to 10.5 ng/mL with chemotherapy.

During the chemotherapy protocol, chest CT scan that was performed after recognizing a swelling at the front side of the chest wall releaved a 4.3 x 3.9 x 4.5 cm size mass which destructed the distal part of the sternum (Figure 4).

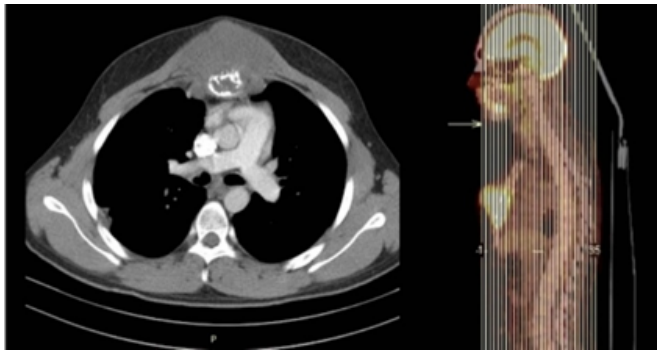

Figure 4. Chest CT showing the mass causing destruction at the distal sternum.

Therefore, screening for whole body positron emission tomography (PET-CT) showed an 7.4 x 6.4 x 8.0 cm size mass which destructed middle and distal part of the sternum and also invaded the medial part of the pectoralis major muscle and showed exophytic elongation to subcutaneous tissue. The level of AFP, which was reduced by about 3 months in the follow-up, increased progressively to a level of 33.591 ng/mL. Based on the increase in AFP levels and the findings of PET-CT, the tumor was decided to be chemotherapy-resistant. In consequence of resistance to chemotherapy, with the decision of the pediatric oncology council, we performed a total sternal resection. The defective area was reconstructed with 10 x 9 cm size polypropylene mesh and titanium rib clips were placed onto 3rd to 5th ribs bilaterally over the polypropylene mesh. Titanium plates were fixed to the rib clips transversely for the stability of the chest wall (Figure 5).

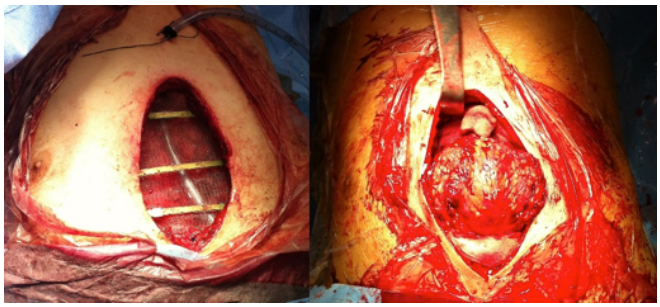

Figure 5. Intraoperative view; sternal reconstruction with titanium plates and polypropylene mesh.

The surface was covered by a pectoralis major flap and skin. Postoperative pathological examination showed destruction in one area of the sternum macroscopically and the malign mixed germ cell tumor invasion microscopically. The patient was discharged at 7th day postoperatively (Figure 6).

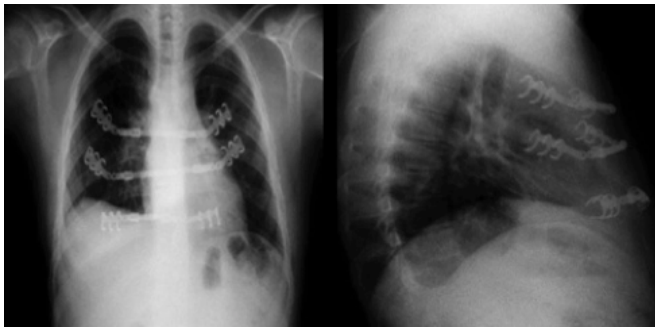

Figure 6. Postoperative posteroanterior and lateral chest X-ray at discharge.

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Chemotherapy protocol was continued with Vinblastine, Adriamycin and Sorafenib. Unfortunately, the patient died by virtue of showing multiple metastasis after 31 months from the first operation.

Discussion

Primary mediastinal GCTs was reported to account 6-24% of mediastinal tumors and 3-4% of all GCTs. PMMGCT is more rare and representing 0.32-2% of all childhood cancers [1,4]. PMMGCTs divided into two groups: seminomas and nonseminomatous germ cell tumors (NSGCT). NSGCT group includes yolk-sac-tumor, embryonal carcinoma, choriocarcinoma, immature teratoma, teratocarcinoma and mixed tumor [5]. Mixed GCT is representing 8.5-9.3% of PMMGCTs [5,6]. Mixed GCT is mostly seen at mediastinum [1,4]. There is bimodal age distribution in PMMGCT. First peak is before age 3 and the second is in adolescent age like our case [6].

GCTs metastasis to lung, liver, bone and brain [2]. Necchi et al. reported 25 (29.1% of all) lung metastasis and 8 (9.3% of all) liver, bone and brain metastasis cases [2]. They suggested chemotherapy after surgery in lung metastasis and performed metastasectomy to 20 patient of lung metastasis cases. They also reported poor prognosis in lung metastatic group [2]. In our case, lung metastasis was seen after 8 month of first diagnosis and metastasectomy was performed.

Due to poor prognosis, a multidisciplinary approach that includes surgery, chemotherapy with or without radiotherapy is advised. Cisplatin-based chemotherapy regimens recommended as the first line therapy. The most commonly used one is VIP (Etoposide, Ifosfamide and Cisplatin) protocol. The Pediatric Oncology Group (POG) and The Children's Cancer Study Group (CCG) are recommending BEP (Bleomycin, Etoposide, Platin) protocol as an alternative treatment. However, when a surgical intervention is necessary for residual tumor, due to lung toxicity of bleomycin, oxygen requirement of the patient could increase [2,5,7]. In case of progression, low response and recurrence second-line chemotherapy is indicated. Commonly cisplatin, etoposide and ifosfamide combinations are used. However, TIP (paclitaxel, ifosfamide, cisplatin), TOG (paclitaxel, oxaliplatin, gemcitabine) and TPG (paclitaxel, cisplatin, gemcitabine) protocols are used in cases which are resistant to therapy [2]. Nevertheless, successful treatment of GCT in childhood required complete resection of the mass, if possible [1,4]. Despite different chemotherapy protocols, there were lung, lymph node and sternal metastasis in our case.

The treatment of the sternal tumors is en-bloc surgical resection [3]. It is also indicated in chemoresistance GCT so we performed metastasectomy for lung lesions and a sternal resection in this case. Wide resection of the sternum will result with a defect. Therefore, sternal reconstruction with a tough prosthesis should be performed to prevent paradoxical respiration and to protect lungs, heart and great vessels from trauma and infection [3,8]. Until today, various of materials including homolog bone, muscle, fascia lata, omental or metallic meshes, polypropylene mesh, polyglycolic mesh, methyl methacrylate and silicon that replaced into two polypropylene or polyglactine patches are used in alone or combined way for sternal reconstruction [3,9]. The most commonly used and the firm one is the "sandwich" method which was formed by methyl methacrylate and silicon that replaced into two polypropylene or polyglactine patches. However, the preparation technique is hard and needs to be experienced. Complications like early breakage, infection and tissue damage with perioperative heat were reported in literature [10]. Recently, the use of titanium plates as a new method for the chest wall reconstruction was reported. Titanium is a non-corrosive material that could be applied by reserving chest wall anatomy and physiology. In addition, it is reported to cause no local infection. Briccoli et al. reported their cases maintains their daily activities after sternal reconstruction with titanium plates [3]. But metallic plates could cause lung injuries because of their affinities to tissue [3,8,9]. To prevent lung injury, Berthet et al. reported their technique by placing polytetraflouroetylene (PTFE) under the plates, otherwise Briccoli et al. achieved it by placing polypropylene mesh [3,9]. Thus, they could prevent tissue affinity of the plates to preserve lungs. Titanium does not disturb the visualization, both for magnetic resonance imaging (MRI) and for CT, without interrupting the oncologic patient's follow up so it could be used in these patients safely [8,9]. We performed sternal reconstruction with titanium plate and polypropylene mesh after sternum resection. The patient maintained daily activities seamlessly in postoperative period.

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Presence of lung metastasis and surgical resection are factors that influence survival in NSGCT [2]. The median survival rates for 3 and 5 years were 47.4% and 23%, respectively [5]. In NSGCTs, the diseases free survival and median survival rates were 59.5% and 71.4%, respectively [6]. Marina et al. reported the mortality risk as 6 times higher in patients who are older than 12 years, in thoracic GCTs [6]. Billmire et al. reported a higher mortality depending on tumor progression in male patients older than 15 years [7]. Our case was 13 years old, the disease showed a rapid progression and was lost at 31 month, postoperatively.

Despite the metastasis to lung, liver, brain and bone, sternal metastasis is rare in PMMGCT. The treatment of PMMGCT and its metastasis are surgical resection, if possible. In case of metastasis to sternum of PMMGCT sternal resection could be performed safely. To obtain an ideal rigidity and biocompatibility, titanium plate and polypropylene mesh can used in sternal reconstructions. Multiple surgical resections to mediastinal germ cell tumors and its metastasis could contribute survival time, if they are resistant to other therapies.

Declaration of conflicting interests

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Review Article

Current advances in early detection, residual disease monitoring and treatment response in lung cancer: Liquid biopsy

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ABSTRACT

Lung cancer exhibits the highest mortality rate of all malignant tumors, and only a minority of non-small cell lung cancer (NSCLC) patients are diagnosed with localized, early stage tumors. Unfortunately, NSCLC is usually detected at advanced and inoperable stages. Tumor biomarkers can detect early stage lung cancer independently or in combination with low-dose computed tomography-based screening techniques. A liquid biopsy is a noninvasive modality for the pathological and molecular characterization of cancer, and it can be isolated from bodily fluids. There are a variety of biological elements that can be isolated from the peripheral blood, such as exosomes, circulating cell-free (tumor) DNA, circulating tumor cells, and microRNA. A liquid biopsy can be used to detect somatic mutations before treatment and dynamically during treatment, and to monitor the treatment response. It can also be used for minimal residual disease quantification, and to determine the emergence of therapy resistance. Despite the numerous research studies showing successful results, clinically available lung cancer biomarkers do not have sufficiently high specificity and sensitivity for widespread use. Therefore, universal experimental and therapeutic research regarding advanced molecular diagnostics has become necessary.

Keywords: biomarker, liquid biopsy, lung cancer

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Introduction

Lung cancer is one of the most frequently diagnosed cancers, and it is the number one cause of death due to cancer worldwide [1]. Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung neoplasms. NSCLC patients with pathological stage IA tumors have a 5-year survival rate of 73%, while stages IIB and IIIB have rates of 36% and 9%, respectively. Unfortunately, the long-term lung cancer survival rate currently remains low, because the majority of the cases are detected at advanced and inoperable stages of the disease [2,3]. Even in cases of complete surgical resection, the 5-year survival probability is unsatisfactory [4,5]. Following patients with thorax computed tomography (CT) scans every 6 months for the first 2 to 3 years after a complete surgical resection has been recommended by the National Comprehensive Cancer Network guidelines [6]. However, recurrence or metastasis occurs in approximately 30%–70% of all complete resection cases [7]. The leading cause of death in cancer patients is metastasis, in which malignant cells spread the primary tumor to distant organs through the blood circulation via a multistep process [8]. A delayed diagnosis and the lack of reliable biomarkers are the main reasons for lung cancer detection in the advanced stages and its high mortality rates [9].

Biological elements are secreted from cancer cells into their microenvironment in order to promote oncogenesis, and to protect themselves from the immune system [10]. A liquid biopsy is a noninvasive strategy for the pathological and molecular characterization of cancer, and it can be isolated from bodily fluids, such as the peripheral blood, cerebrospinal fluid, pleural fluid, urine, and saliva [11,12]. In this review, we will discuss the roles of liquid biopsies in lung cancer, while evaluating the potential biomarkers for early detection, residual disease monitoring, and the treatment response.

Early lung cancer detection

Significant efforts have been made to determine new screening methods for early lung cancer detection, early treatment, and survival improvement [13]. In a high-risk population, the most commonly used lung cancer screening and early detection method is thoracic low-dose CT (LDCT). This method was recommended by the National Lung Screening Trial, which demonstrated the LDCT efficacy for detecting lung cancer, resulting in a 20% reduction in patient mortality when compared to those patients screened using conventional chest x-rays [14,15]. However, there are many LDCT screening limitations, and, as an inefficient diagnostic tool, it has a high false positive rate of 96.6%. These false positives can lead to excessive medical care, unnecessary invasive diagnostic procedures, increased deaths from avoidable surgeries, and psychological overload [16]. In addition, LDCT is associated with recurrent radiation exposure, which can lead to the development of radiation-induced lung cancer [17].

Tumor or cancer biomarkers can be used to detect early stage lung cancer independently or in combination with the LDCT-based screening techniques used for selecting high-risk patients to undergo further diagnostic examinations. They can help increase the proportion of complete surgical resections, which is the most effective curative therapy for local tumors [18]. In order to be as effective as a clinical or early diagnostic device, the biomarker must be present in the bodily fluids, be measurable and reliable, and show a high sensitivity and specificity to the disease being studied [19]. Despite the numerous screening outcomes with successful results, the clinically available lung cancer biomarkers do not have sufficiently high specificities and sensitivities for widespread use [20].

Lung cancer diagnosis

Although a tumor tissue biopsy is the most reliable method for diagnosing cancer in clinical medicine, it is an invasive procedure, it is often unattainable, and it has various limitations in clinical practice [11,21]. A conventional needle biopsy, bronchoscopy, thoracentesis, or other invasive method is required to obtain a sufficient number of samples, depending on the disease site. This usually provides inadequate material, and it represents a single snapshot of the tumor. When the tissue obtained is sufficient for a histopathological analysis, a definitive diagnosis is more likely. However, even if a sufficient biopsy can be obtained, it is an unreliable method in cases of heterogeneous and continuously evolving tumors, because it increases the patient's risk and discomfort when collecting repetitive samples [21,22].

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It is always difficult and sometimes impossible to obtain tumor tissues from patients in order to monitor the tumor dynamics, because most diagnostic procedures are invasive, and the patients dislike repeated approaches. In addition, tumor heterogeneity is subject to selection bias. Moreover, especially for patients suffering from a relapse after receiving chemotherapy or targeted therapy, the original somatic mutation may change [15,23]. Nosaki et al. [24] reported that the rebiopsy rate using an invasive method had overtaken that of the initial biopsy rate (7.8% vs. 1.8%). The median rebiopsy duration was 12.5 days, suggesting that cooperation between the surgical and radiology departments is mandatory. A rebiopsy can expose a patient to a greater risk of complications and delayed results; therefore, the use of noninvasive diagnostic procedures can avoid causing additional distress to the patient [22].

Potentially, a liquid biopsy could be used for a variety of clinical and investigational applications, and lately, the literature has shown that it is a reliable method for the noninvasive evaluation of tumor-specific biomarkers [25]. A liquid biopsy has several advantages, such as its feasibility for collecting multiple specimens at various points before and during treatment, heterogeneous resistance mechanisms, and wider representation of the entire genomic landscape by monitoring tumor genomic changes over time (including the primary tumor and multiple metastatic sites) [11]. When detecting a mutation in a liquid biopsy, one cannot say conclusively that it belongs to the lung mass seen in the imaging. However, although these mutations cannot be distinguished from a second primary metastatic malignancy, they can strengthen the diagnosis of primary lung cancer [26].

There are a variety of biological elements that can be isolated from the peripheral blood, including exosomes, cell-free DNA/circulating tumor DNA (cfDNA/ctDNA), circulating tumor cells (CTCs), and microRNA (miRNA). Additionally, a liquid biopsy also includes tumor-educated platelets (TEPs), tumor-associated antigens (TAA), and tumor-associated autoantibodies (TAAb) [8,12,27,28]. The ctDNA certainly represents the most experiential element of a liquid biopsy in clinical practice with regard to lung cancer patients. Both ctDNA and exosomes carry many characteristics of the tumors from which they arise. They have provided promising results as biomarkers, and they preserve much of the valuable molecular information [29]. However, there are many difficulties associated with this approach, such as the presence of small amounts of secreted tumor components, short half-lives, cell/DNA fragmentation, high tumor cell mutation variation, and tumor source identification failure [30].

a. Exosomes

Exosomes (also called extracellular vesicles) of 40–100 nm in size were first discovered by Johnstone et al. [31] in 1987, and they have been described as microvesicles with 5'-nucleotidase activity. They are produced from multivesicular bodies and released from neoplastic and other cells into the extracellular space and a variety of bodily fluids [32]. Exosomes consist of lipids, proteins, and nucleic acids (DNA, as well as coding and noncoding RNA) from tumor cells, and indicate many tumor characteristics, such as the status of the cells from which they originate and the cellular mechanisms that they engage in [33]. Being relatively stable, they are ideal candidates for liquid biopsy diagnoses [34]. Exosomes play important roles in the proliferation of cancer cells, along with their primary duty in exosome-mediated communication within the tumor environment by transferring biomacromolecules to targeted cells modulating the activities of the recipient cells [34,35].

Exosomes can be selected with the presence of specific protein markers, such as the tetraspanin proteins CD63, CD9, and CD81, and they can also be extracted from body fluids by normal density-gradient centrifugation or ultracentrifugation and visualized by transmission microscopy [12,36]. Rabinowits et al. showed that the circulating tumor exosome levels (exosomal small RNA and exosomal miRNA specific for lung adenocarcinoma) were higher in lung adenocarcinoma patients when compared to a healthy group [37]. Therefore, one might obtain information about a disease's pathology and prognosis through the exosomal miRNA's disease-specific gene signature [38].

Exosomal miRNA is enriched in the circulatory system, and it is protected from RNase degradation, when compared to the circulating miRNA. When the exosomes are extracted, the contents (miRNA) can be investigated using different techniques, including the reverse tran-

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scription polymerase chain reaction (RT-PCR), sequencing, Western blot, or enzyme-linked immunosorbent assay (ELISA), for somatic mutation, splice variant, gene fusion, and gene or protein expression profiling. As a potential diagnostic biomarker and important mediator of drug resistance, exosomal miRNA has been investigated broadly in lung cancer cases [39].

Jin et al. [40] demonstrated a unique pattern of expression between stage I adenocarcinoma and squamous cell carcinoma (SCC) patients paired with healthy individuals. They used miRNA sequencing to extensively profile tumor-derived exosomal miRNA, and the miRNA profiles showed sensitivities of 80.65% and 83.33% and specificities of 91.67%, and 90.32% for the adenocarcinoma and SCC diagnoses, respectively. Based on these results, one can conclude that for diagnosing NSCLS at an early stage, miRNA is a highly sensitive, noninvasive, and promising biomarker.

Despite the promising results mentioned above, different cell types can release exosomes; therefore, an exosomal miRNA clinical application for an early NSCLC diagnosis is challenging. Other bodily fluids, including pleural effusion, can be used to isolate exosomes in cancer patients [41].

b. cfDNA /ctDNA

Mandel and Metais discovered the presence of circulating cfDNA in the late 1940s [42]. Small fragments of DNA are secreted into the blood circulation from every living cell, and the mechanisms of an increased ctDNA concentration include apoptosis and necrosis, as well as the lysis of viable tumor cells [43]. cfDNA is described as any DNA that is freely circulating in the blood, while ctDNA is the proportion of cfDNA that is specifically released from tumor cells [44]. Because of the ctDNA's tumor specificity, it can provide a real-time evaluation for specific mutations and diagnostic and prognostic assessments [45,46]. Between malignant and benign diseases, there is a significant difference in the circulating DNA plasma concentrations [47]. Leon et al. [48] discovered that the cfDNA occurred at a much higher level in the blood of cancer patients. After the discovery of ctDNA, a liquid biopsy analysis has become a noninvasive method to diagnose and monitor tumor evolution over time in clinical practice. Cancer patients are of specific interest for exploring the potential of liquid biopsy substitutes for tissue biopsies, because ctDNA detection can mitigate the need for invasive tissue biopsies [12]. A liquid biopsy can also be used to monitor changes during the natural course of the disease or during cancer treatment with the ease of repeated blood sampling [49].

Before its application, there are several challenges, including the major challenge of determining the sensitivity and specificity of ctDNA detection due to its scarcity in the blood when compared to the cfDNA from normal cells [50]. Some studies demonstrated that the quantification and analysis of the cfDNA in the blood during the early disease stages was challenging due to the very low concentration (approximately 0.01%–1%) of the ctDNA fraction [51]. The traditional ctDNA analytic approaches can be broadly divided into amplification and sequencing-based methods. Moreover, highly sensitive blood-based assessments have been developed and used extensively to test the cfDNA at very low concentrations in order to detect ctDNA point mutations. These consist of polymerase chain reaction (PCR)-based techniques [digital PCR, droplet digital PCR, real-time quantitative PCR (qPCR), and peptide nucleic acid clamp-based PCR], beads, emulsions, amplification, and magnetics (BEAMing), pyrophosphorolysis-activated polymerization, and next-generation sequencing technologies. Unfortunately, the methods based on DNA amplification cannot be applied as routine diagnostic tools, because they are time-consuming, expensive, and require large-volume samples (> 5 ml) [51,52]. Hu et al. [53] reported the use of nanomaterials as biosensors in patient serum samples for ultrasensitive ctDNA detection. With this strategy, the treatment responses and patient monitoring both during and after treatment have shown promising results.

Other studies have demonstrated elevated ctDNA levels in cancer patients, as well as the correlation of these levels with the tumor disease burden, tumor response, and survival outcome [54,55]. One study about cfDNA quantification showed that the plasma DNA concentration, as determined by the qPCR of the human telomerase reverse transcriptase gene, was almost eight-times higher in the patients with lung cancer than in the patients with cigarette smoking histories and those at high risk for lung cancer development. Therefore, for

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patients with a higher risk, this assay is an extremely sensitive and specific noninvasive approach [55]. Newman et al. [56] also determined that the cfDNA levels were significantly correlated with the tumor volume, and that it is possible to detect disease progression earlier when using them than when using radiological approaches. However, if the structure of the tumor tissue and the expected mutations are not known in advance, the role of cfDNA genotype scanning for somatic mutations remains unknown.

c. Methylation

Some studies have reported that tissue-specific DNA can be identified using the methylation information of the circulating DNA. Methylation-based epigenetic markers are promising for the early detection of lung cancer [57,58]. DNA methylation is necessary for a living cell to function, and it is a naturally occurring process. However, because DNA methylation can also occur in the normal tissue surrounding the tumor, the specificity of methylated DNA as a biomarker may be low [11].

Hypermethylation has been shown in cancer patients, and it functions via gene alteration regulation to promote carcinogenesis [59]. Methylated DNA is remarkably stable, it generally exists during the early stages of carcinogenesis, and it can be found in different bodily fluids [59,60]. Even though the epigenetic changes are not unique for any tumor, the methylation of promoter regions within the genomic cytosine-guanine islands leads to gene expression regulation and gene silencing [61]. Moreover, some tumor suppressor genes are frequently methylated and downregulated in specific tumors, which could be useful for determining the diagnosis and prognosis [61]. In 2010, Bailey et al. [62] revealed an efficient and reproducible method for detecting methylation markers from small quantities of DNA in the circulating blood.

d. CTCs

Ashworth described the presence of CTCs in the bloodstream of cancer patients for the first time in 1869 [63]. CTCs are detached from primary tumor sites and/or metastatic sites to circulate in the bloodstream, where they can be found as either single cells or clusters, and they contribute to cancer progression and metastasis development. CTCs are closely associated with the tumor size, progression, metastasis, relapse, and prognosis [64,65]. Some previous studies have suggested that CTCs could be used as biomarkers for determining the prognosis and predicting and monitoring the treatment response [65,66]. When compared to ctDNA, a CTC analysis provides the opportunity to study whole cells that contain DNA, RNA, and protein-based molecular profiling [67].

Thus far, the only US Food and Drug Administration approved CTC detection system for prognostic purposes in metastatic breast, colorectal, or prostate cancer is CellSearch (Veridex, LLC., Raritan, NJ, USA) [68,69]. In early diagnosis, CTCs can be missed because of their low concentration in the blood (1–10 CTCs per 10 ml), epithelial to mesenchymal transition, and downregulation of epithelial markers during progression [70]. Another antibody-mediated capture technology, the CTC-chip, has detected CTCs in metastatic tumors, including lung cancer, at a rate of almost 100%, and in the peripheral blood of patients with solid tumors with approximately 50% purity [69,71]. In lung cancer, different techniques have been used to detect CTCs and evaluate their roles; however, the clinical application of CTCs as predictive and prognostic biomarkers is still under investigation. Moreover, the value of CTCs in NSCLC patients has not yet been determined due to the lack of standardization for the current methods [72].

e. miRNA

miRNA is a small noncoding RNA gene product that ranges between 19 and 22 base pairs, which regulates gene expression by binding to specific targeted messenger RNA (mRNA) sequences. It plays a key role in modulating various cellular processes, including proliferation, cell migration, and apoptosis, and it has also been implicated in several pathological phenotypes. The most common cell-free RNA (cfRNA) molecule in the blood is miRNA [12,73,74], which can be carried in exosomes, apoptotic bodies, protein-miRNA complexes, and TEPs [12]. miRNA serves as a tumor suppressor and oncogene in cancer cells [75].

Different cancer types are associated with different miRNA expression patterns, and the structure of the miRNA in the circulating blood is similar to that of a primary solid tumor [76]. Indeed, the let-7 family is a novel biomarker for lung cancer [77]. In one study eval-

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uating miRNA as a potential biomarker for NSCLC, the diagnostic value of a plasma miRNA set, including miRNA-21, miRNA-126, miRNA-210, and miRNA-486-5p, revealed 86.2% sensitivity and 96.55% specificity. Additionally, the study reported that altered expressions were previously confirmed in lung tumor tissues [78]. miRNA is highly stable in the blood, and thus, it may become an ideal biomarker for lung cancer detection [79].

f. Other biomarkers

Many other biomarkers can be obtained from liquid biopsy samples, and these could be used for the early detection and screening of lung cancer. During the early stages of lung cancer, TAAs, such as the carcinoembryonic antigen, carbohydrate antigen (CA) 125, CA199, neuron specific enolase, and cytokeratin 19 fragment 21-1, are rarely released into the bloodstream. Because of their poor sensitivities and specificities, they cannot detect the various heterogeneous lung cancer types [80]. However, TAAbs, which are autoantibodies against overexpressed, mutated, misfolded, or aberrant autologous cellular antigens, are very stable, and they can be detected at high levels during the early stages of lung cancer [81]. Sullivan et al. [82] conducted the largest lung cancer screening program with 12,000 participants in Scotland. It consisted of a randomized controlled trial of patients at high risk of developing lung cancer, and it was run based on a 7-AAb panel.

Hemostasis is the main role of the platelets, but they may be a good platform for detecting rearrangements and for diagnosis, because, apart from hemostasis, they play outstanding roles in the systemic and local responses to tumor growth [83,84]. Platelets take up the tumor-related RNA released from tumor cells via several microvesicle-dependent or independent mechanisms, resulting in TEPs [85]. In addition, platelets pass through specific pre-mRNA assembly in response to the activation of the platelet surface receptors, leading to a unique mRNA profile that could possibly be used for a cancer diagnosis [86].

Postsurgical and treatment response monitoring

The standard method for analyzing the genetic changes in cancer tissue is a repeated tumor biopsy. However, this is an invasive and impractical technique that often results in an insufficient tissue sample [87].

Recurrence and metastases may develop in approximately 30%–50% of NSCLC patients [88]. After surgery, routine biomarker monitoring using a liquid biopsy could reveal recurrence 1 to 2 years earlier than a radiographic screening, as well as reveal those who would benefit from certain therapy types (i.e. chemotherapy and radiotherapy) [89]. A liquid biopsy can be used to determine somatic mutations before treatment, and dynamically during treatment, enabling the quantification of the minimal residual disease and emergence of therapy resistance, as well as monitoring the therapy response. Recently, many studies have focused on dynamic CTCs/ctDNA monitoring to predict a relapse as soon as possible. The results have shown that the ctDNA, with a higher sensitivity, was more favorable and reliable than the CTCs [11,12,90].

Although the lung cancer survival rate is low, molecularly targeted therapies for gene alterations, such as the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS1, have radically changed the treatment approach and prognosis of the disease [91,92]. However, the long-term efficacy of these agents is limited by tumor heterogeneity, leading to multiple resistance mechanisms being developed during targeted therapy [92,93]. In Turkey, gene sequence analyses for ALK, KRAS, BRAF, ROS1, EGFR, and MET using cfDNA are being conducted at the medical genetics departments of certain universities.

Lung cancer treatment has dramatically evolved over the last decade, mainly because of the clinical use of targeted and personalized therapies. Since lung cancer is a highly heterogeneous disease, certain patients do not respond to a targeted agent while having an activated oncogene, and some are faced with rapid disease progression, although they showed an initial objective response [94].

In clinical practice, the plasma genotyping for EGFR sensitizing or T790M-mutations through cfDNA extraction can predict the response to EGFR and EGFR-tyrosine kinase inhibitor (EGFR-TKI) therapy, and it can monitor the resistance possibilities [95]. Approximately 50%–60% of the patients with EGFR mutations in exon 20 (T790M) exhibit progression while undergoing treatment with EGFR-TKIs due to therapy resistance [96].

Tumors can resist autoimmune antitumor activity by

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modulating immune checkpoint inhibitors and immune checkpoint proteins, like programmed death ligand 1 (PD-L1) and programmed cell death 1 (PD-1) [97]. The expression of PD-L1 is elevated in many types of cancer, and it often goes along with the tumor mutational burden, suggesting a poor prognosis and predicting the response to targeted therapy drugs [98,99]. A tissue biopsy shows only a snapshot of the PD-L1 expression, while a liquid biopsy has the ability to dynamically examine the whole molecular picture of the tumor tissue by using CTCs as a substrate for the analysis, because PD-L1 is a dynamic biomarker that can be induced by targeted therapy, chemotherapy, or radiation therapy [100]. Immunotherapy has become an effective approach for the treatment of NSCLC, and regulatory agencies in both the US and EU have already approved PD-L1/PD-1 immunotherapy [101].

Fusion genes, which encode fusion proteins, generate noncoding RNA, and contribute to tumor progression, are caused by aberrant chromosomal translocations [102]. NSCLC cases exhibit the echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion gene at a rate of approximately 4%–5%. EML4-ALK translocation activates ALK-TKI and generates tumor proliferation, migration, and invasion [103]. Veldore et al. [104] recommended that targeted therapy could be used for 8%–10% of all the EGFR mutation-negative NSCLC patients who have translocations in EML4-ALK, ROS1-ALK, and KIP4-ALK.

Overall, it has become mandatory that universal experimental and therapeutic research regarding advanced molecular diagnostics be done to solve common resistance mechanisms with the development of next-generation agents.

As a conclusion, although a tissue biopsy is still the accepted standard for diagnosing lung cancer, a liquid biopsy can offer an alternative or supportive technique when a tissue biopsy is insufficient or unobtainable. The development of analytical technologies and the knowledge gained from large-scale sequencing projects have provided possibilities for individualized diagnoses and targeted drug treatments. Combining a liquid biopsy with a tumor biopsy could introduce additional qualifications toward improvements in NSCLC patient management. With the growing interest in molecular testing in every field of cancer, liquid biopsies have shown considerable promise for compiling precious information about cancer genetic alterations in almost real time. We strongly believe that there is an urgent need for biomarkers with high accuracy, which might improve early stage lung cancer detection, predict the treatment response, and anticipate tumor relapses that are not yet visible on imaging. In addition, they can provide a rapid and dynamic assessment of progressive resistance mechanisms.

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