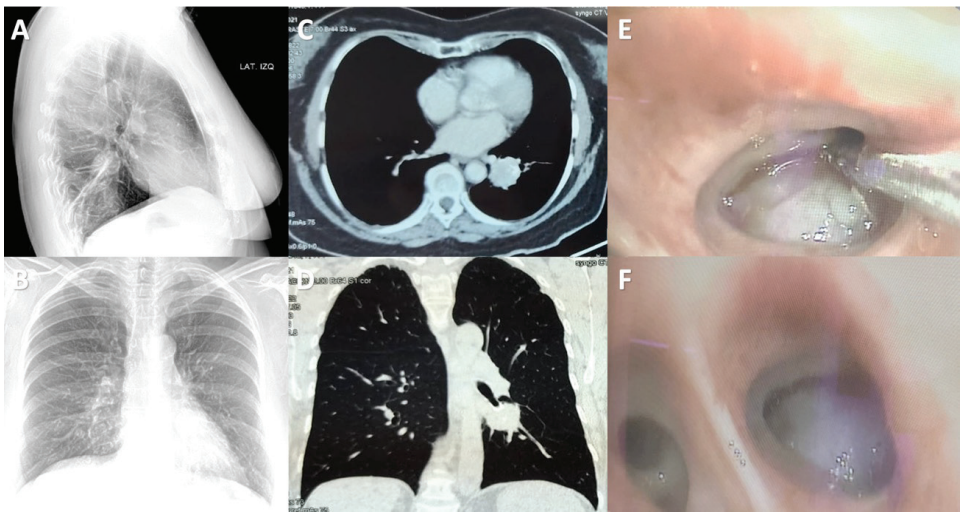
Volume 8 Number 3 December 2023 eISSN 2548-0316

CURRENT THORACIC SURGERY



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Curr Thorac Surg

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Volume 8 **Number 3** **December 2023** **eISSN 2548-0316**

Volume 8 Number 3 December 2023 eISSN 2548-0316

International Editorial Board

Table of Contents

Volume 8 Number 3 December 2023 eISSN 2548-0316

Original Articles

117 **Does lung cancer histology affect the efficacy of talc pleurodesis through pleural catheter?**
Melike Badoglu, Hüsnü Baykal

122 **Did COVID-19 anxiety cause a delay in the patients' decision to be operated on for lung malignancy?**
Seda Kahraman Aydın, Tiffany Melissa Ergin Onar, Tevfik Ilker Akcam, Ufuk Cagirici, Ali Ozdil

128 **Chest wall reconstructions with synthetic prosthetic materials**
Seray Hazer, Necati Solak, Leyla Nesrin Üstün, Pınar Bıçakçıoğlu, Göktürk Fındık,Selim Şakir Erkmen Gülhan

136 **Postpneumonectomy bronchopleural fistula: cohort of patients in a Pevurian National Hospital**
Karin Gonzales-Peña, W Samir Cubas, Pamela Villanueva-Zúñiga

143 **Pathological diagnoses and adenosine deaminase levels in patients undergoing pericardial window operation for large pericardial effusions**
Ayfer Utkusavas, Murat Akkus, Ilker Kolbas, Hande Ikitimur

Case Report

148 **Video-assisted thoracoscopic surgery lobectomy with guillotine stapler technique for the second primary adenocarcinoma of the lung after immunotherapy**
Dilara Gürsoy, Özgür Samancılar, Kutsal Turhan

151 **Pulmonary carcinoid tumor of endobronchial presentation: a case report**
Mayra Valderrama-Saldaña, W Samir Cubas, Helen Reina, José Somocursio, Max Small

155 **First awake uniportal video assisted thoracoscopic lobectomy in Turkey**
Volkan Karaçam, Gönül Sağıroğlu, Emrah Karcı, Fatma Mutlu, İlkay Kaya

160 **Tuberous sclerosis and chylothorax**
Burcu Oksuz Gungor, Sami Karapolat, Omer Topaloglu, Atila Turkyilmaz

To cite this article: Badoglu M, Baykal H. Does lung cancer histology affect efficacy of talc pleurodesis through pleural catheter? Curr Thorac Surg 2023 Aug; 8(3): 117-121. doi: 10.26663/cts.2023.0021. CTSID: 1001. Online ahead of print.

Original Article

Does lung cancer histology affect the efficacy of talc pleurodesis through pleural catheter?

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ABSTRACT

Background: Up to 50% of lung cancer patients develop pleural effusion during the course of the disease. Dyspnea is the primary indication for intervention. After drainage, chemical pleurodesis may be applied. Talc is the most effective sclerosing agent, and sometimes the procedure may not be successful. Adults, histologically confirmed lung cancer patients with pleural effusion who had talc pleurodesis through pleural catheter between 2014 and 2019 were included. The aim was to clarify whether lung cancer histological type and talc pleurodesis efficacy were correlated or not.

Materials and Methods: A total 222 patients were enrolled retrospectively. Through the study; age, sex, cancer histological type, pleural/pleural effusion FDG uptake in PET/CT, pleural effusion's location, amount, biochemical property, and pleurodesis efficacy were recorded.

Results: Mean age was 65.52 years, 22.9% of them were women, and 73.3% were men. Lung cancer histological types were; small cell lung cancer (13.1%), adenocarcinoma (72.1%), squamous cell carcinoma (9.5%), and not specified non-small cell lung cancer (5.4%). In 22.1% of the patients, pleurodesis was efficient, in 50% partially efficient, and in 27.9% inefficient. The only independent factor affecting pleurodesis efficacy was found as cancer histological type ($p < 0.05$). Pleurodesis efficacy was found higher in the squamous cell carcinoma group ($p < 0.05$).

Conclusions: As far as we know, this is the first study on correlation between efficacy of talc pleurodesis through the pleural catheter and the lung cancer histological types. Pleurodesis was significantly more efficient in patients with squamous cell carcinoma, possibly due to its immunohistochemical behavior.

Keywords: lung cancer, malignant pleural effusion, pleurodesis efficacy, talc pleurodesis

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E-mail: drmelikeb@gmail.com Phone: 00905302410822
Doi: 10.26663/cts.2023.0021
Received 22.05.2023 accepted 18.08.2023

Introduction

Malignant pleural effusion (MPE) represents 660 million incidence and almost half of the cases are caused by lung cancer, which is the most common cause. Up to 15% of lung cancer patients have MPE, and up to 50% will develop it during the course of [1]. When the effusion is massive, depending on the patients' respiratory reserve, it might cause or aggravate dyspnea symptom which worsens the life quality and hospital admissions. Malignant pleural effusion also affects these patients' prognosis and survival in a bad way [2]. Especially in recurrent and massive malignant pleural effusion, drainage is made for symptom palliation, and sclerosing agents may be applied into the pleural space to prevent recurrence. Chemical pleurodesis is a procedure which is applied to create symphysis between visceral and parietal pleura. Almost all agents induce a nonspecific organizing pleuritis that leads to pleural fibrosis, talc also elicits histolytic and granulomatous foreign body reaction [3, 4]. Talc is the most effective and most well studied sclerosing agent [4, 5]. Talc may be applied via thoracoscopy, through the chest tube, and through the pleural catheters [6-8]. However, sometimes the procedure does not succeed and patients admit to hospital with recurrent pleural effusions. To evaluate the pleurodesis efficacy complete response/efficacy, partial response/efficacy and no response/poor efficacy terms are identified. Complete response/efficacy is when no pleural effusion is observed again, partial response/efficacy is when pleural effusion is significantly (>50%) decreased, no response/poor efficacy is when effusion is larger than defined by the partial response [9]. In a study of Rafei et al, pleurodesis efficacy was found as 17.7%, partial success as 12.9% and inefficacy as 40.3% [10]. Chen et al found that thoracoscopic talc pleurodesis was less successful in patients with lung adenocarcinoma than other histological types [9]. No other published study was found in the literature that focuses on correlation between histologic lung cancer type and pleurodesis efficacy.

In general clinical practice in our center, talc pleurodesis is applied through a small diameter pleural drainage catheter (Pleuracan®) in patients diagnosed with malignant pleural effusion due to lung cancer. There is no published study about the correlation between lung cancer histopathologic type and the efficacy of talc pleurodesis through pleural catheter. Aim of this study is to clarify whether histological lung cancer type and pleurodesis efficacy/inefficacy are correlated or not.

Materials and Methods

Adults, histologically confirmed lung cancer patients with pleural effusion who had talc pleurodesis through a small diameter pleural drainage catheter (Pleuracan®, B. Braun, Melsungen Germany) in our center between 2014 and 2019 were included in the study. Patients under 18 years of age, not have pathologically confirmed lung cancer, not develop pleural effusion, not have pleural catheter applied, not have talc pleurodesis applied for malignant pleural effusion, and patients who had pleurodesis because of indications other than pleural malignant pleural effusion (such as pneumothorax and surgical resection), were excluded. The flow diagram for patient selection is shown in Figure 1.

A total of 222 patients who had inclusion criteria were researched from the hospital database and patient files retrospectively. Age, sex, histological type of lung cancer (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and not specified non-small cell lung cancer), pleural/pleural effusion FDG uptake in PET/CT (>2.5, <2.5), pleural effusion location (right, left), pleural effusion amount (moderate, massive), biochemical property of effusion (exudate, transudate), and pleurodesis efficacy (efficacy, partial success, inefficacy) were recorded.

Pleurodesis was applied when pleural fluid drainage through a small diameter pleural drainage catheter (Pleuracan®) was less than 100 ml for last the 24 hours, as talc slurry through Pleuracan®, with 4 grams of in 50 cc 0.9% NaCl solution to all study population. The catheter was clamped for 1 hour after the procedure and removed when radiological re-expansion was seen.

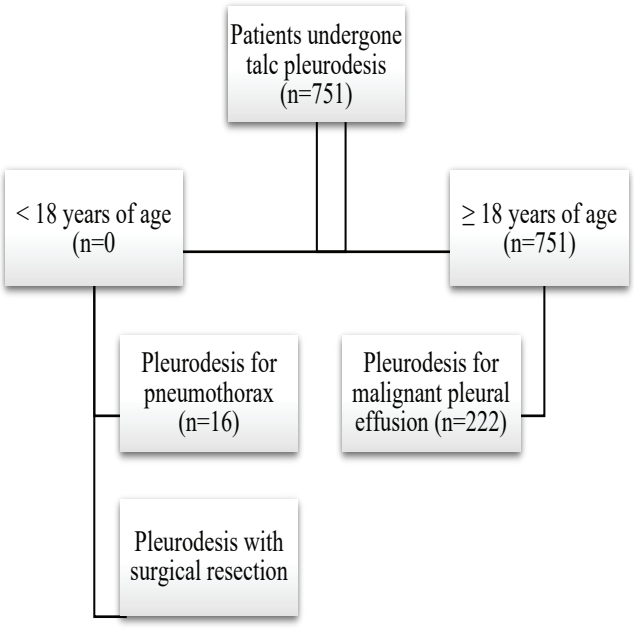

Figure 1. Flow diagram for study enrollment.

To define pleurodesis efficacy, like other studies in literature, these criteria were used; successful/efficient pleurodesis: No recurrent pleural effusion develops after pleurodesis, partial efficiency: 50% and less amount of previous pleural effusion recur after pleurodesis, unsuccessful/inefficient pleurodesis: More than 50% amount of previous pleural effusion recurs after pleurodesis [9,10].

Patients were grouped in three due to their pleurodesis efficacy, and in four due to their histological lung cancer type.

The patients were checked for pleurodesis efficacy firstly on the 30th, 60th, 90th days after the procedure, and also before chemotherapy, at routine cancer control dates, and/or in case of any pulmonary symptom for their all lifelong. The study was approved by the Ethics Committee of University of Health Sciences, Ankara Atatürk Sanatorium Training and Research Hospital.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) for Windows, Version 22.0. Armonk, NY: IBM was used for the statistical analysis. Quantitative variables' mean, standard deviation, median, lowest and highest values, frequency and rate of the categorical variables were calculated by descriptive statistics. The distribution of variables was controlled with the Kolmogorov-Smirnov test. ANOVA test was used for the analysis of lung cancer histological types' and other categorical parameters' effect, Independent samples T test was used for effect of age on pleurodesis efficacy. Finally, logistic regression analysis (LRA) was performed to find out independent factors for pleurodesis efficacy. $P < 0.05$ was accepted as statistically significance for all statistical analyzes.

Results

The mean age of 222 patients was 65.52 years (min 30, max 88). Fifty-three of them (22.9%) were women, 169 were (73.3%) men. 13.1% of the patients had small cell lung cancer (SCLC), 72.1% of them had adenocarcinoma, 9.5% had squamous cell carcinoma, and 5.4% had not specified non-small cell lung cancer (NOS). Demographic data of the study population is shown in table 1.

The pleurodesis efficiency rate was found 22.1%, in 50% (n = 111) of patients it was partially efficient and in 27.9% (n=62) the pleurodesis was found inefficient.

ANOVA and independent T-test were performed to determine the parameters' effect on pleurodesis efficiency. Lung cancer histological type was found to be the only factor that affects pleurodesis efficiency (p = 0.002) (Table 2).

Table 1. Demographic data of the patients enrolled.

	Mean±standard deviation (sd)	Minimum value	Maximum value
Age	65.62±10.16	30	88
			%
Sex	Female	53	23.87
	Male	169	76.13
Lung cancer histological type	SCLC	29	13.06
	Adenocarcinoma	160	72.07
	Squamous cell carcinoma	21	9.45
	NOS	12	5.40
Pleural involvement	Positive biopsy	85	38.28
	Negative biopsy	14	6.30
	No biopsy	123	55.40
Pleural effusion FDG in PET/CT	≥2.5	144	64.86
	<2.5	78	35.13
Pleural effusion localization	Right hemithorax	130	58.56
	Left hemithorax	92	41.44
Pleural effusion amount	Non-massive	153	68.92
	Massive	69	31.08
Pleural effusion biochemistry	Exudate	214	96.39
	Transudate	8	3.61
Pleurodesis efficacy	Efficient	49	22.07
	Partially efficient	111	50
	Inefficient	62	37.93

In regression analysis, the only independent factor affecting pleurodesis efficacy was found out as the cancer histological type (p = 0.006).

Post-hoc regression test was used to find out which histological type/s was/were prognostic for pleurodesis efficiency. Pleurodesis was found to be two times more efficient in patients with squamous cell carcinoma (p = 0.038). The worst pleurodesis efficiency was found in the NOS group (p = 0.029). The statistical results are shown in table 3.

Table 2. Risk factors for pleurodesis efficiency.

	P
Age	0.076
Sex	0.062
Lung cancer histological type	0.002*
Pleural involvement	0.144
Pleural effusion FDG in PET/CT	0.594
Pleural effusion localization	0.473
Pleural effusion amount	0.092
Pleural effusion biochemistry	0.61

** p<0.05 was accepted as statistically significance.*

Table 3. Predictive histological factors for pleurodesis efficiency.

	Efficient pleurodesis		Partially efficient pleurodesis		Inefficient pleurodesis	
	OR(CI%95)	P	OR(CI%95)	p	OR(CI%95)	P
SCLC	1.109(0.455, 2.702)	0.409	1.288(0.681, 2.438)	0.218	0.458(0.155, 1.359)	0.079
Adeno	0.667(0.348, 1.279)	0.111	1.266(0.747, 2.148)	0.19	0.947(0.509, 1.764)	0.432
SCC	2.153(0.919, 5.046)	0.038*	0.274(0.107,0.709)	0.003*	1.025(0.395, 2.063)	0.479
NOS	0.744(0.161, 3.439)	0.352	0.168(0.037,0.769)	0.01*	2.481(0.966,6.376)	0.029*

** p<0.05 was accepted as statistically significance*

Discussion

Patients in this study mostly had adenocarcinoma (72.1%), 13.1% of the patients had small cell lung cancer (SCLC), 9.5% of them had squamous cell carcinoma, and 5.4% had no NOS diagnosis, histologically. This result was also compatible with the literature. Duzcu and Ozturk found that lung adenocarcinoma was the most common etiology in malignant pleural effusion, lung small cell carcinoma was the second, and lung SCC came in third place in their seven-year retrospective study on pleural fluid cytology [11]. Also in a review of MPE studies, histological type distribution in MPE complicating lung cancer was found as adenocarcinoma 78-82%, squamous cell carcinoma 14-25%, small cell carcinoma 44-53%, and miscellaneous 0-47% [12].

In the study of Rafei et al, pleurodesis efficacy was found to be 17.7%, partial success was 12.9% and inefficacy was 40.3% [10]. Our sample's pleurodesis success was higher than that. In our study, in 22.1% of patients, pleurodesis was efficient, 50% had partial success, and pleurodesis was inefficient in 27.9%. In a meta-analysis, no difference in pleurodesis success was found between large and small chest tubes [13]. While our sample included only patients with lung cancer, patients in Rafei's study had primary tumors in several organs. Tumor origin might be the main cause of different success rates.

Chen et al found that thoracoscopic talc pleurodesis was less successful in patients with lung adenocarcinoma than other histological types [9]. We found out that patients with squamous cell carcinoma had a significantly higher efficient pleurodesis rate. In patients with nonsquamous histological types, pleurodesis was less successful and the least successful pleurodesis was in the NOS group, but we did not find a significant difference in the adenocarcinoma group. However, the techniques of pleurodesis were different in the studies.

To the best of our knowledge, this is the first study that researches the correlation between the efficacy of talc pleurodesis through the pleural catheter and the lung cancer histological types. Pleurodesis was 2 times more efficient in patients with squamous cell carcinoma, possibly due to immunohistochemical behavior.

The limitations of the study were its retrospective nature and the absence of analysis about the effect of patients' comorbidities and medications on pleurodesis efficacy.

In conclusion, this study investigates the correlation between the efficacy of talc pleurodesis through a pleural catheter and lung cancer histological types. The only independent factor affecting pleurodesis efficacy was the lung cancer histological type, and pleurodesis was 2 times more efficient in patients with squamous cell carcinoma compared to other histological types, possibly due to immunohistochemical behavior differences. With those evidences and the literature data, we

strongly believe that immunohistochemical studies defining efficient and safe biological or targeted agents are needed to improve talc pleurodesis efficacy in different types of lung cancer patients with MPE.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethics approval

The study was approved by Ethics Committee of University of Health Sciences, Ankara Atatürk Sanatoryum Training and Research Hospital (Approval number 2012-KAEK-15/2687, on 26.04.2023).

Authors' contribution

MB: Concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review, HB: Data acquisition, data analysis, manuscript editing and manuscript review

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Current Thoracic Surgery

To cite this article: Kahraman Aydın S, Ergin Onar TM, Akcam TI, Cagirici U, Ozdil A. Did COVID-19 anxiety cause a delay in the patients' decision to be operated on for lung malignancy? Curr Thorac Surg 2023 Aug; 8(3): 122-127. doi: 10.26663/cts.2023.0022. CTSID: 959. Online ahead of print.

Original Article

Did COVID-19 anxiety cause a delay in the patients' decision to be operated on for lung malignancy?

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ABSTRACT

Background: With the COVID-19 pandemic, "corona anxiety and phobia" negatively affect people in various fields which can lead patients to delay even their lung cancer operations. It was investigated whether the reason was COVID-19 phobia in patients who wanted to postpone lung surgery, and it was aimed to evaluate the COVID-19 anxiety scores in these patients.

Materials and Methods: Between April 2020 and January 2022, the data of patients who were recommended to be operated on due to lung malignancy, but who reported that they wanted to postpone the surgery were analyzed retrospectively. The patients were contacted by phone and questioned whether the reasons for the postponement were the COVID-19 pandemic. The patients were evaluated in the context of the "Coronavirus Anxiety Scale (CAS)" and their anxiety scores and reasons for delay were analyzed with CAS scores.

Results: Of the 122 patients who were recommended to be operated on due to lung malignancy, 90 were operated on, while 32 patients (26.2%) postponed the operation. The mean surgery delay time was 11.59 ± 7.13 months, it was detected that the mean anxiety score was 2.47 ± 2.46 (0-9) points. The average anxiety score of those who answered "no" to the questionnaire was 0.79 points, those who answered "partially" had 2.69 points, and those who answered "yes" were 6.60 points. The CAS score was significantly higher in patients who reported that they postponed their surgeries mainly due to COVID-19 ($p < 0.001$).

Conclusions: Higher levels of coronavirus anxiety were detected in patients who reported that they postponed lung surgery due to COVID-19.

Keywords: coronaphobia, coronavirus anxiety, delay, lung cancer, surgical treatment

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Doi: 10.26663/cts.2023.0022
Received 22.01.2023 accepted 22.05.2023

Introduction

The new type of SARS-CoV-2 epidemic, which emerged in Wuhan, China in December 2019 and spread in a short time in all regions, was defined as a "Coronavirus-19 or COVID-19 pandemic" by WHO in March 2020 [1,2]. Over the past 24 months, more than 500 million people are reported to have been infected, and more than six million to have died from COVID-19. Although most of the people all over the world are fully or partially vaccinated, the threat to humanity of the COVID-19 pandemic due to variant viruses continues.

As of January 20, 2020; the date on which COVID-19 was reported to be transmitted from person to person, strict quarantine measures began to be taken in all countries, especially in China. Negative psychological effects were observed as a result of the decrease in economic and social mobility with the introduction of home isolation rules [3]. Fear of being infected and dying, as well as the fear of not being able to find resources for basic needs and access to health services, emerging as an anxiety and phobia associated with COVID-19 [4,5]. In the context of COVID-19 being a specific source of anxiety, the "Coronavirus Anxiety Scale" (CAS) was developed to demonstrate its measurability [6]. The Turkish validation of the CAS also carried the strong psychometric properties of the test [7].

When isolation rules became a part of life, people had a dilemma about applying to the hospital for basic health problems. When the patients for whom an operation decision was made, were called at the appropriate time, and called for hospitalization, they began to state that they wanted to postpone their surgeries for varying periods or plan them when the pandemic ended (although it is known that there is an indefinite time frame).

In the study, it was aimed to evaluate the correlation with CAS in patients who were recommended to be operated for lung malignancies, but who gave up or postponed their admission to the hospital due to COVID-19 anxiety.

Materials and Methods

Patients with a diagnosis or suspicion of lung malignancy are listed in the thoracic surgery service. Considering the availability of the clinic and the risk to the patient, patients are called to the service by calling for hospitalization at the appropriate time. Patients who were called for surgery between April 2020 and January 2022, but who postponed their hospitalization for any reason (gave up hospitalization / reported that they were undecided), were documented. Cases with the diagnosis of psychiatric disorders excluded from the study. Patients were called by phone and asked whether the reason for the postponement or cancellation of hospital admission was related to COVID-19 (Yes/partly/no). The patients were then evaluated in the context of CAS. The CAS consists of five questions, each scored from zero to four (Table 1). High scores between zero and 20 points are correlated with the patient's COVID-19 anxiety. The information about whether the patients were vaccinated against COVID-19 and if so, how many doses were recorded. For this study local ethics committee approval was obtained (Approval decision 22-5T/44).

Table 1. Coronavirus Anxiety Scale [6,7].

How often have you experienced the following activities over the last 2 weeks?		Not at all	Rare, less than a day or two	Several days	More than 7 days	Nearly every day over the 2 last weeks
1	I felt dizzy, lightheaded, or faint, when I read or listened to news about the coronavirus.	0	1	2	3	4
2	I had trouble falling or staying asleep because I was thinking about the coronavirus.	0	1	2	3	4
3	I felt paralyzed or frozen when I thought about or was exposed to information about the coronavirus.	0	1	2	3	4
4	I lost interest in eating when I thought about or was exposed to information about the coronavirus.	0	1	2	3	4
5	I felt nauseous or had stomach problems when I thought about or was exposed to information about the coronavirus.	0	1	2	3	4
Column Totals		____ +	____ +	____ +	____ +	____ +
Total Score ____						

Statistical Analysis

IBM SPSS Statistics 25.0 Program was used. The conformity of the numerical variables to the normal distribution was examined using the Shapiro-Wilk ($n < 50$) test. Numerical variables were given as mean and standard deviation and (min-max). Mann-Whitney-U test was used since the comparison of the two groups in terms of numerical variables could not be compatible with the normal distribution.

The Kruskal-Wallis Test was used because the normal distribution was not suitable for comparison of more than two groups in terms of numerical variables. Categorical variables were given as numbers and percentages. The relationship between categorical variables was examined using Pearson Chi-square and Fisher's exact Chi-square tests. The relationship between numerical variables was examined by Spearman correlation analysis. The significance level of $p < 0.05$ was be accepted for all hypotheses.

Results

Of the 122 patients who were recommended to be operated with a pre-diagnosis of lung malignancy, 90 were operated, while 32 patients (26.2%) postponed the operation. Among this patient group, seven patients were operated in the later period. 20 (62.5%) of the 32 patients were female and 12 (37.5%) were male. The mean age was calculated as 57.3 ± 15.9 (22-82) years. Seven of the patients (21.8%) were operated on, albeit with a delay. In non-operational patients, between enrollment in the operation list and calling patients for the study were considered a delay period. The mean delay time was 11.59 ± 7.13 (1-25) months. When the anxiety scores were examined, a mean score of 2.47 ± 2.46 (0-9) was found.

When the parameters that could affect the anxiety scores were analyzed, the mean score of COVID-19 anxiety was 2.10 ± 2.38 (0-9) points in women and 3.08 ± 2.57 (0-9) points in men. Gender difference was not found to be significant in terms of COVID-19 anxiety.

To the question of whether the reasons for postponing their surgeries were related to COVID-19, 14 people (43.8%) said "no"; 13 people (40.6%) "partially"; 5 people (15.6%) answered "yes". The mean anxiety score of those who answered "No" was 0.79 ± 1.12 (0-3); the mean score of those who answered "partially" was 2.69 ± 1.43(0-6); and the average score of those who answered "yes" was 6.60 ± 2.30 (4-9) points. The COVID-19 anxiety score was significantly higher in patients who postponed their surgeries mainly because of the pandemic and partially because of the pandemic, compared to those who postponed their surgeries for other reasons ($p < 0.001$) (Table 2).

No correlation was found between anxiety scores and latency times. The majority of those included in the study were patients for whom surgery was recommended due to an undiagnosed lung nodule (n=30, 93.75%). Of the two diagnosed patients, one was squamous cell carcinoma, and the other was unsub typed non-small cell lung carcinoma (NSCLC). The patient with a diagnosis of squamous cell carcinoma answered "no" to the question of whether the reason for the postponement was related to COVID-19, while her/his anxiety score was zero. The patient with NSCLC answered "partially" to the question of whether the reason for postponement was due to COVID-19, and her/his anxiety score was two. It was thought that the patients might have postponed the surgery by considering the possibility of the undiagnosed lesions being "benign", but the patient group was not suitable for comparative statistical analysis.

Ten patients (31.25%) did not want to share their vaccination status or information could not be obtained. When 22 patients whose vaccination information could be accessed were evaluated, four patients (18.18%) were not vaccinated, and 13 patients (59.09%) were vaccinated at three or more doses.

Table 2. Demographic data and Anxiety Scores.

Gender	n (%)	anxiety score (mean±std.dev.)	p
Female	20 (62.5)	2.10	
Male	12 (37.5)	3.08	0.129
Age			
≥ 65	15 (46.8)	2.13±2.7	
< 65	17 (53.2)	2.76±2.7	0.756
Is the reason for delay is Covid-19?			
No	14 (43.8)	0.79±1.12	No vs. partially (0.016*)
Partially	13 (40.6)	2.69±1.43	No vs. yes (< 0.001*)
Yes	5 (15.6)	6.60±2.30	Partially vs. yes (0.101)

*Abbrev.; Std.dev.: Standard deviation; vs.: Versus; *: Statistically significant*

Discussion

It is known that having an oncological disease is a predisposing factor for psychiatric disorders [8]. The susceptibility of cancer patients to psychiatric diseases such as depression, stress disorder and generalized anxiety decreases the quality of life by adding to somatic pathologies [9]. In a study, it has been shown that patients diagnosed with lung cancer are under the risk of anxiety up to 37% and depression up to 44% [10].

It has been shown that COVID-19 infections course in patients with lung malignancies are mortal compared to the population and patient population with non-pulmonary malignancies [11]. An analysis of patients who contracted COVID-19 after lung surgery found that resection of five segments or more was closely associated with death. The incidence of severe COVID-19 was higher in damaged lungs [12].

Health-related anxieties may increase or decrease depending on many variables, and both conditions may cause problems [13]. Increased anxiety during the pandemic may result in frequently applying to health institutions or refraining from going to health institutions even when needed [14]. In a study in which a positive correlation was found between hospital anxiety and corona phobia, psychiatric support and encouraging strategies were suggested to prevent the interruption of treatment processes of cancer patients [15]. Psychological counseling has been shown to reduce depression and anxiety scores [16].

When Fujita et al. evaluated lung cancer patients who were in the medical treatment process, they reported that 9.1% of the patients experienced disruption and delay in treatment due to the pandemic [17]. The fact that most of the patients postponed the treatment voluntarily suggested that the anxiety of COVID-19 was higher than expected. While the delay of treatment is requested, even if it is medical; considering that possible complications can be extremely mortal, it seems understandable that patients want to postpone their surgeries.

While it has been reported in the literature that women have higher COVID-19 anxiety scores, gender was not found as a determining parameter in our study [18].

Since the first vaccine was administered in Turkey in January 2021, 52 million people (52%) received a double dose, and 26 million (42.5%) received three doses (Republic of Turkey Ministry of Health Covid-19 Vaccination Information Platform, March 2022). The fact that cancer patients feel more vulnerable to COVID-19 and want to be protected from the disease has increased vaccination rates [19]. In our study, 18 (81.81%) of the patients (n = 22) whose information could be accessed were vaccinated and thus reported that they felt partially safe compared to before vaccination. Statistically significant analysis of the anxiety score difference between vaccinated and unvaccinated was not possible, as there were only four unvaccinated subjects.

Although the results showed that COVID-19 anxiety could be effective in delaying patients who were planned for lung resection, the study had some limitations. Since it was unethical to invite patients to the hospital only for inclusion in the study, telephone communication was preferred. The fact that the Likert-type scale in CAS could not be shared visually with the patients may have created a deficiency. Answering the questions face-to-face made it necessary for us to feel and repeat whether the patients understood the questions with sharp clarity.

In the pandemic conditions, economic concerns as well as health anxiety may have been effective in delaying surgeries. Using the "COVID-19 Phobia Scale (C19P-S)" which is developed by Arpaci et al and which includes psychological, psychosomatic, economic, and social questions, could have provided wider research. However, this scale consisted of 20 questions and it was thought that it would be difficult to get a healthy answer over the phone when the duration of the survey was extended [20].

In a study in which COVID-19 related treatment delays were investigated including urology patients, it was found that postponing surgery in urooncology patients increased anxiety and depression scores [21]. While fighting a pandemic that primarily affects the lungs; planning for surgery due to or suspected lung cancer is a major source of stress for patients. Patients who are afraid of the pandemic enter an indefinite waiting period. It has been reported that delayed treatment procedures result in more complications in patients receiving medical treatment [22,23]. Whilst non-malignant elective surgeries were held up during the pandemic, we did not postpone oncological surgical interventions due to the possibility of increase in the stage of malignancy. When patients who are included in the lobectomy plan are delayed, extended resections may come to the fore due to the advanced disease. The average delay of almost one year in our study suggests that some of these patients may have lost their

chance of operability. While leaving the decision to have the surgery or postpone it to the patient, it seems important to clearly explain the complications that may be encountered in both situations [24].

In conclusion, it was observed that the COVID-19 anxiety scores were high in patients who voluntarily postponed the operation due to lung cancer in the last one and a half years. Considering the delayed surgical treatment of these patients, we can predict that we will encounter high complication rates when the pandemic slows down. Comprehensive studies are needed to objectively state the extent to which delays affect the progression of lung cancer. We are of the opinion that psychological support, vaccination procedures, and access to accurate information in order to cope with the anxiety of COVID-19 in patients with high-risk lung cancer or suspected can reduce complications due to delays.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethics approval

Approval was obtained from the Local Ethics Committee of Ege University (Approval Decision 22-5T/44).

Authors' contribution

SKA; design and writing the paper, TMEO; collecting and processing data, TIK; critical review, UC; conceptualize and supervision; AO; critical review.

Acknowledgement

We would like to thank Mr. Cüneyt Evren, M.D for sharing the "Coronavirus Anxiety Scale" that forms the basis of our study.

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To cite this article: Hazer S, Solak N, Üstün LN, Bıçakçıoğlu P, Fındık G, Gülhan SŞE. Chest wall reconstructions with synthetic prosthetic materials. Curr Thorac Surg 2023 Aug; 8(3): 128-135. doi: 10.26663/cts.2023.0023. CTSID: 997. Online ahead of print.

Original Article

Chest wall reconstructions with synthetic prosthetic materials

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ABSTRACT

Background: Chest wall tumors can be malignant and benign and present as primary or metastatic lesions. For the definitive treatment of malignant thoracic wall tumors, the surgical margin should be established at a distance of at least 4 cm from the tumor. A 1-2 cm distance from the tumor is often sufficient in benign or low-grade malignancies. Repairing the deformity with prosthetic materials in 3 or more rib resections (>30 cm) is recommended. In resections containing four or more ribs, the mesh should be supported with metallic rib bars screwed to the periphery of the defect.

Materials and Methods: Thoracic wall resection was performed on 285 patients between 2008 and 2019 in the Department of Thoracic Surgery of Ankara Atatürk Sanatoryum Training and Research Hospital. Repair with prosthetic graft was performed in 70 cases, and thoracic wall resection was performed in 215 patients without using mesh. The results of 50 patients who underwent thoracic wall reconstruction with a prosthetic graft were evaluated retrospectively.

Results: The female/male ratio in those using mesh is 0.47; the mean age is 52.5 (14-76 years); the tumor size (mean long diameter) is 11 cm (4-18 cm); the number of removed ribs is 2.5 (1-5 pieces) is Sternal resection was performed in 2 patients, sternum resection in 1 patient, left clavicle partial resection, right clavicle partial resection, and first and second ribs of the left side resection. Partial excision of the clavicle and first rib was performed in 1 patient. Polypropylene mesh in 28, PTFE mesh in 20, and polyglactin mesh in 2 patients were used. The mean postoperative hospital stay was 10.6 days (2-58 days), and the mean follow-up period was 16.6 months (0-96 months, median 7 months). Complications developed in 10 patients (20.0%). Three patients underwent revision surgery; one was operated on for empyema at four months, and the patch was removed. The others were performed at the 16th and 30th months due to recurrence. Mortality developed in 4 patients in long-term follow-ups.

Conclusions: Polypropylene mesh can cause wrinkles and folds as it shows less stretch when suturing than Polytetrafluoroethylene (PTFE). In addition to the difficulties of providing a smooth surface, it also causes the passage of fluid and air in the pleural space from the pores to the subcutaneous space. PTFE patches are frequently used, non-permeable, flexible, high tissue compatibility, durable and robust, but poor body wall integration has been reported. Polypropylene and PTFE mesh comparison results are similar to the literature. Suppose a significant defect (>30 cm2) exists in patients who have undergone thoracic wall resection; reconstruction should be performed to stabilize the thoracic wall, prevent lung hernia, paradoxical breathing, mediastinal structures, and intrathoracic dislocation of the scapula, and provide aesthetically appropriate rib cage contours.

Keywords: chest wall, reconstruction, polyprolen mesh, PTFE, thoracic surgery

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Doi: 10.26663/cts.2023.0023
Received 12.05.2023 accepted 28.08.2023

Introduction

Chest wall entirety and stability are the primary aspects that protect intrathoracic organs and adequate respiratory function. Following the resection of the rib or sternum with soft tissue, chest wall reconstruction commonly requires adding components to provide chest wall stability and coverage with well-vascularized soft tissue. Repairing skeletal stability is essential to diminish the negative effect on respiratory function [1,2]. The goals are avoidance of lung hernia, paradoxical chest wall motion, scapular impaction into the defect in posterior chest wall resections, and protection of the underlying mediastinal organs in anterior chest wall resections with providing an aesthetically pleasing chest contour. The location, size, depth of the defect, the viability of the surrounding tissue, and prior operative procedures determine the optimal approach to reconstruction [3]. Defects >5 cm in diameter or including >3 ribs should be reconstructed due to the increased risk of lung herniation and respiratory compromise from the paradoxical movement of the chest wall, particularly valid for anterolateral defects and total thickness resections[3,4]. The reconstruction of chest wall defects with prosthetic material depends upon defect size and location. The resections that include three or more ribs (more than 30 cm2) typically require reconstruction. Some apical-posterior defects, even 10 cm in size, do not require reconstruction because of the scapula and shoulder girdle support, except for defects lower than the fourth rib posteriorly, with the tip of the scapula at risk of entrapment[3,4]. The fundamental need for skeletal reconstruction for more minor defects has been inquired. [6,7].

Synthetic mesh sutured beneath tension supplies an adequately rigid chest wall repair that decreases ventilator support and hospitalization [8]. Since using synthetic mesh, rigid reconstruction utilizing autologous rib grafts or semirigid fascial grafts has evolved less commonly; these require a donor site harvest. The superior synthetic mesh should be rigid enough to underestimate paradoxical chest wall motion, porous enough to allow tissue ingrowth, and malleable, radiolucent, and inert [9]. Autologous grafts may still be utilized if a synthetic mesh is not readily obtainable or the wound is at an increased risk of infection.

This study aims to evaluate surgical outcomes of chest wall reconstruction, focusing on synthetic materials in chest wall tumors regarding early mortality, complications, and length of hospital stay.

Materials and Methods

Between 2008 and 2019, 285 patients who underwent thoracic wall resection in our clinic were evaluated retrospectively. The patients were evaluated in age, gender, clinical features, the surgical method applied, defect size, prosthetic material, pathological diagnoses, length of hospital stay, complications, recurrence, and mortality. Patients whose adequate information could not be accessed in the system were excluded from the study.

All patients were evaluated with preoperative chest x-ray and thorax CT. Thoracic CT-guided transthoracic biopsy was taken for patients without a previous pathological diagnosis. Pet CT in malignant patients was used for staging, and invasion was evaluated preoperatively with thoracic MR in patients with suspected close tissue invasion. CT and MR imaging determined the tumor's location, depth, and invading tissues. The margin for tumor resection was determined preoperatively, and which soft tissues, bone structures, and lung tissues should be removed. Bone and soft tissue were resected 3 cm away from the tumor, with the negative margin being the most critical. Because giant tumors often invade the thorax, ribs, pleura, and even some lung tissue, these components often need to be resected to achieve R0 incised margins.All patients were transferred to the ICU after the operation.

We operated on patients whose tumor was considered completely resectable as long as their general medical condition allowed surgery. All cases were reviewed by a multidisciplinary team (MDT) before surgery. Neo-adjuvant chemotherapy was prescribed according to the MDT decision, and MDT reassessed adjuvant treatments (chemotherapy and radiation) according to the primary diagnosis, surgical outcomes, and final pathological report. This study was approved by the Ankara Atatürk Sanatoryum Training and Research Hospital institutional Ethics Committee (No: 2710/2023).

Results

Chest wall resection was performed on 285 patients between January 2008 and December 2019 in the Department of Thoracic Surgery of Ankara Atatürk Sanatoryum Training and Research Hospital. Prosthetic grafts were used in 70 cases, and 215 patients underwent thoracic wall resection without using mesh. The results of

fifty patients who underwent thoracic wall reconstruction with a prosthetic graft were included for evaluation retrospectively. Twenty patients who underwent prosthetic material were excluded from the study because they did not meet the inclusion criteria for reasons such as being unable to access their information or being unfollowed. Twenty patients were excluded due to did not meet the inclusion criteria.

All patients were considered with chest X-rays and thorax CT. Thoracic CT-guided transthoracic biopsy was taken for patients without a diagnosis. PET/CT in malignant patients was used for staging, and invasion was estimated preoperatively with thoracic MR in patients with suspected, immediate tissue invasion. All patients received preoperative standard antibiotic prophylaxis.

The female/male ratio in those using mesh is 0.52; the mean age is 54.34 (14-76 years), and the tumor size is 10.66 cm (4-18 cm).

The most frequent malignant tumors were squamous cell carcinoma (n: 14, 28%), adenocarcinoma (n: 6, 12%), and chondrosarcoma (n: 4, 8%). Preoperative chemotherapy was administered in 19 malignant patients, and 27 had adjuvant chemotherapy.

The benign diseases were fibrous dysplasia (n: 5, 10%), osteochondroma (n: 1, 2%), tuberculosis (n: 1, 2%), (the diagnosis of the patients indicated in Table 1).

The mean long diameter and the number of removed ribs is 2.70 (1-5 pieces).In addition to chest wall resection, lobectomy was performed in 22 patients, thymectomy in 1 patient, and pericardial resection with the diaphragm in 1 patient. The sternum was resected in 4 patients, and the clavicle was resected in 2. Polypropylene mesh in 28 (56%), PTFE mesh in 20 (40%), and polyglactin mesh in 2 patients (4%) were used. The mean postoperative hospital stay was 9.87 days (2-39 days), and the mean follow-up period was 16.6 months (0-96 months, median 7 months).

Postoperative complications developed in 10 patients (20%). Wound infection developed with prolonged air leakage in 2 patients with PTFE mesh and was treated with debridement antibiotics and wound care. Chylothorax (n: 1) occurred on the 2nd day and was treated with conservative treatments. Serous wound drainage with subcutaneous emphysema (n: 2, polyprolene mesh) developed and was treated with conservative treatment. In contrast, empyema occurred in a patient with PTFE on the 9th day, and another had empyema in the fourth month. The first patient was treated with antibiotics and tube thoracostomy; the other patient occurred in the fourth month, underwent surgery for mesh removal. One patient with prolonged air leakage underwent bulla resection with VATS on the fifth day. One patient with polypropylene mesh due to bleeding (on the second day) underwent a re-thoracotomy to evacuate the hematoma.

After falling from high, a 20-year-old male patient was referred to our hospital for hemopneumothorax, and a parenchymal mass with chest wall invasion was detected in exploration with thoracotomy incidentally. Chest wall resection and reconstruction were performed with PTFE mesh (Figure 1). The histopathological diagnosis was Ewing Sarcoma/ primitive neuroectodermal tumor.

Late revision surgery was performed for three patients; one was operated on due to empyema in the 4th month and mesh removed, and others were operated on for recurrence in the 16th and 30th months.

A patient with squamous cell carcinoma had respiratory distress due to pulmonary thromboembolism on the 12th day and was deceased. In addition, three patients were deceased during follow-up. One died due to MHRS pneumonia after chemotherapy in the third month, one died due to respiratory distress due to recurrent thymoma in the sixth month, and another died in the ninth month due to lung adenocarcinoma metastasis to the contralateral lung and brain. Demographics and overall survival of the patients are mentioned in Table 2.

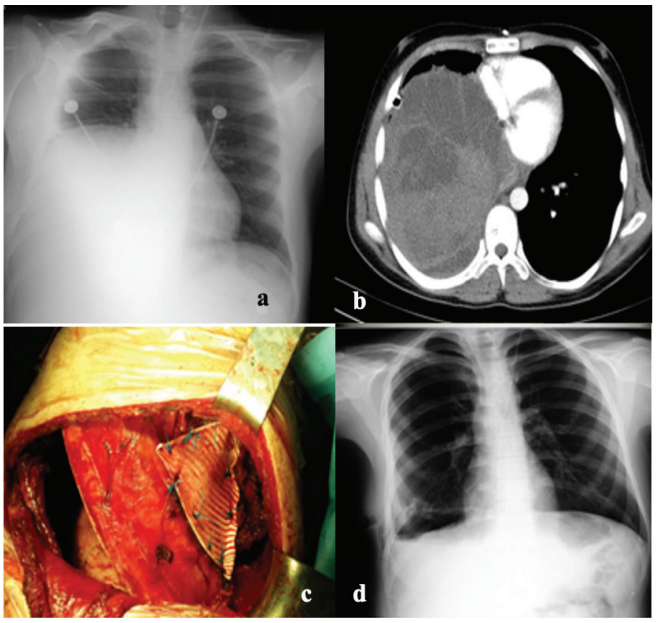

Figure 1. 20-year-old male patient presented with a left lower lobe mass (Ewing Sarcoma). Preoperative chest x-ray and CT showing the mass, located in the right lower lobe **(a,b)**, due to the invasion of the chest wall, resection and reconstruction with PTFE mesh were performed **(c)**, postoperative chest x-ray of the patient **(d)**.

Table 1. Diagnosis of the patients who underwent chest wall reconstructions with synthetic mashes.

Diagnosis	Number of Cases	Frequency (%)
Squamous Cell Carcinoma	14	28
Adenocarcinoma	6	12
Fibrous Dysplasia	5	10
Chondrosarcoma	4	8
Malign Mesenchymal Tumor	2	4
Liposarcoma	2	4
Plasmocytoma	2	4
Fibromatosis (Desmoid tumor)	2	4
Osteochondroma	1	2
Osteosarcoma	1	2
Adenocarcinoma + large cell neuroendocrine carcinoma	1	2
Thymoma infiltration	1	2
Ewing sarcoma	1	2
Hemangioma	1	2
Indiferential sarcoma	1	2
Malign fibrosis histiocytoma (Pleomorfic undifferential sarcoma)	1	2
Osteomyelitis, hydatic disease	1	2
Carcinosarcoma squamous cell Carcinoma (Squamous cell carcinoma + chondrosarcoma)	1	2
Tuberculosis	1	2
Breast cancer	1	2
Malign mixed germ cell tumor (Yolk Sac + embriyonel carcinoma)	1	2

Discussion

A fundamental principle preliminary to the initiation of the chest wall reconstruction is a proper and thorough chest wall resection that leaves healthy, viable margins to which materials and tissues used in a reconstruction may be anchored securely. Detailed preoperative assessment for the spread of disease in patients with primary or metastatic malignancies is necessary before chest wall resection or reconstruction, especially for patients with breast and lung cancer locally invading the chest wall and in patients with metastatic disease to the ribs or sternum.

The treatment principle of chest wall malignant tumors is to reach a negative margin by radical resection, extend the survival time, and decrease the mortality and postoperative recurrence rate [9,10]. Most patients undergoing primary chest wall resection will have some postoperative respiratory dysfunction. However, the severity is often less than that following trauma. Therefore, in extra to routine laboratory tests, pulmonary function tests (i.e., spirometry) should be acquired preoperatively to determine the patient's candidacy for the offered resection and to provide a comparison for postoperative comparison [11,12]. Negative margins are an important predictive factor for local recurrence rate. For high-grade, aggressive, or highly infiltrating malignancies, wide local excision with 4 cm margins is usually indicated; however, resection in an individual patient depends on the type of tumor and anatomic location. 1 to 2 cm margins are generally sufficient for benign processes and low-grade malignancies [2]. Repair of skeletal stability is critical to reducing the adverse effects on respiratory function. The purposes include preventing pulmonary herniation, paradoxical chest wall motion, scapular impaction into the defect during posterior chest wall resections and defense of underlying mediastinal organs in anterior chest wall resections by reaching an aesthetically pleasing chest silhouette [1]. Synthetic mesh sutured under tension supplies an adequately rigid chest wall repair that reduces ventilator reliance and hospital stay. While the recurrence rate in negative surgical margins is 10%, it increases to 75% in positive surgical

Table 2. Demographics of the patients who underwent reconstruction with synthetic prosthetic materials.

Patient No	Gender	Age	Diagnosis	Mesh	Resected Chest Wall Area	Size of resection (Long diameter-cm)	Hospital Stay (Day)	Complication	Mortality	Follow-up Duration (Months)
1	Male	52	Adenocarcinoma	PTFE	3, 4, 5 ribs	8	21	Expansion defect and Prolonged Air Leakage	0	1
2	Male	57	Squamous Cell Carcinoma	PTFE	3, 4 ribs	17	14	0	0	3
3	Male	30	Chondrosarcoma	PTFE	2, 3, 4 ribs	5	6	0	0	6
4	Female	14	Osteosarcoma	PTFE	4, 5, 6, 7, 8 ribs	12	9	0	0	2
5	Male	76	Liposarcoma	PTFE	2, 3 ribs	18	6	0	0	5
6	Male	70	Squamous Cell Carcinoma	PTFE	10th rib	6	10	0	0	2
7	Female	60	In-differentient Sarcoma	PTFE	1, 2, 3, 4, 5 ribs	13	11	Wound infection, Expansion defect	0	24
8	Female	21	Fibromatosis	PTFE	2, 3 ribs	9	7	Wound infection, Expansion defect	0	7
9	Male	67	Squamous Cell Carcinoma	PTFE	8, 9, 10 ribs	14	7	0	EX	3
10	Male	66	Adenocarcinoma	PTFE	8, 9, 10 ribs	9	7	0	0	39
11	Male	70	Squamous Cell Carcinoma	PTFE	4, 5 ribs	11	6	0	0	41
12	Male	20	Ewing Sarcoma	PTFE	9, 10, 11 ribs	15	13	0	0	24
13	Male	76	Squamous Cell Carcinoma	PTFE	2, 3 ribs	7	8	0	0	47
14	Male	39	Plasmasitoma	PTFE	Sternum	8	14	0	0	1
15	Female	42	Fibrous Dysplasia	PTFE	6, 7, 8 ribs	17	7	0	0	48
16	Female	39	Chondrosarcoma	PTFE	1st rib+ Clavicle	8,5	8	0	0	17
17	Female	52	Adenocarcinoma	PTFE	6, 7, 8 ribs	14	7	0	0	58
18	Male	58	Squamous Cell Carcinoma	PTFE	7, 8, 9 ribs	8	14	0	0	9
19	Male	72	Liposarcoma	PTFE	3, 4, 5, 6 ribs	18	6	0	0	63
20	Female	52	Tuberculosis	PTFE	7, 8, 9 ribs	9	6	0	0	9
21	Male	64	Squamous Cell Carcinoma	Prolene	8, 9 ribs	10	10	Chylothorax	0	7
22	Female	64	Squamous Cell Carcinoma	Prolene	4, 5, 6, 7 ribs	13	4	0	0	11
23	Male	57	Adenocarcinoma	Prolene	2, 3, 4 ribs	15	7	0	EX	9
24	Female	58	Hemangioma	Prolene	5, 6, 7 ribs	10	7	0	0	38

25	Male	62	Squamous Cell Carcinoma	Prolene	Sternum+ left Clavicle+ right clavicle+ 1st, 2nd ribs	14	7	0	0	4
26	Male	61	Adenocarcinoma	Prolene	7th rib	10	6	Prolonged Air Leakage	0	1
27	Male	55	Adenocarcinoma+Large Cell Neuroendocrine Ca	Prolene	4, 5, 6 ribs	5,5	15	0	0	6
28	Female	59	Fibrous Dysplasia	Prolene	2, 3 ribs	8	8	0	0	24
29	Male	55	Carcinosarcoma (Squamous cell Ca+Chondrosarcoma)	Prolene	7, 8, 9 ribs	5,5	10	0	0	9
30	Female	63	Fibrous Dysplasia	Prolene	3th rib	4,5	8	0	0	17
31	Male	67	Malign Mesenchymal Tumor	Prolene	7, 8 ribs	10	17	0	0	22
32	Male	52	Adenocarcinoma	Prolene	4th rib	5	2	0	0	6
33	Male	64	Squamous Cell Carcinoma	Prolene	4, 5 ribs	8	12	Pulmonary thromboembolism	EX	1
34	Male	53	Squamous Cell Carcinoma	Prolene	5, 6, 7 ribs	4	6	0	0	6
35	Male	14	Malign Mix Germ Cell Tumor	Prolene	Sternum	12	7	0	0	8
36	Female	72	Chondrosarcoma	Prolene	2, 3, 4 ribs	9	7	0	0	12
37	Female	34	Osteochondroma	Prolene	7, 8 ribs	10	6	0	0	36
38	Male	62	Malign Mesenchymal Tumor	Prolene	7, 8 ribs	13	11	Serous Wound drainage	0	2
39	Male	46	Fibromatosis	Prolene	7, 8 ribs	18	6	0	0	2
40	Female	31	Fibrous Dysplasia	Prolene	3, 4, 5 ribs	16	10	0	0	7
41	Male	47	Fibrous Dysplasia	Prolene	1 2 3 4 5 sternum	18	8	0	0	2
42	Male	40	Thymoma	Prolene	4, 5, 6 ribs	11	39	Empyema	ex	6
43	Male	72	Squamous Cell Carcinoma	Prolene	3, 4, 5 ribs	9	20	Serous Wound drainage	0	3
44	Female	53	Squamous Cell Carcinoma	Prolene	2, 3, 4 ribs	10	8	0	0	96
45	Male	70	Chondrosarcoma	Prolene	6, 7, 8 ribs	6	14	Hematoma	0	2
46	Male	67	Osteomyelitis, Hydatid Disease	Prolene	7, 8, 9 ribs	7,5	13	0	0	24
47	Male	70	Plasmasitoma	Prolene	6, 7 ribs	11	8	0	0	14
48	Female	63	Malign Fibrous Histiocytoma	Poligclacin	7, 8 ribs	11	6	0	0	18
49	Male	56	Squamous Cell Carcinoma	Poligclacin	6, 7, 8, 9 ribs	15	12	0	0	48
50	Female	53	Breast Cancer	Prolene	Sternum	7,8	19	0	0	2

margins. For this reason, resection margins should not be compromised with the concern of closing the defect [13]. In our study, recurrence developed in 4 (8%) patients in the thoracic wall resection and reconstructions performed by preserving the negative surgical margin. Two patients (4%) were re-operated for recurrence. Thymoma recurred in 1 patient (2%) and adenocarcinoma in the other patient; both were deceased.

Primary sarcoma and recurrent breast cancer mainly involve the chest wall. Primary chest wall tumors are frequently chondrosarcoma and fibrosarcoma, accounting for about 77.8% of all cases [14]. In the study, chest wall invasion and metastasis rates due to lung cancer were high in our patients who underwent chest wall reconstruction (42%). Chest wall reconstruction was performed in 1 patient (2%) due to breast cancer infiltration. We attribute that a small number of patients were operated on for breast cancer because our center is not multidisciplinary.

The preferred semirigid material for extensive chest wall repairs is synthetic mesh (e.g., polypropylene, polytetrafluoroethylene). Mesh is less rigid than polymethylmethacrylate (PMMA), which is rarely used [15-18] and economical but can extend in the long term with laxity developing at the repair site. Besides, when a mesh is positioned directly in contact with the viscera, such as the lung or exposed bowel (e.g. when the diaphragm requires partial resection), or when the operative site has been irradiated, the risk of complications is increased [20] Synthetic mesh is contraindicated in contaminated wounds.

In our current experience, we do not use methylmethacrylate grafts because it is allergic and more likely to be rejected by the body. In cases where we had thoracic wall resection, we preferred a PTFE patch as much as possible due to lower air and fluid permeability. Prolene mesh is permeable due to punched structure, so the area must be supported with a pedicled muscle graft.

Compared to Polytetrafluoroethylene, Polypropylene mesh causes wrinkles and folds due to less stretching while suturing and the difficulties of providing a smooth surface and the passage of fluid and air in the pleural space from the pores to the subcutaneous area (Figure 1). PTFE patches are frequently used, impermeable, flexible, high tissue compatibility, durable and robust, but poor body wall integration has been reported [21]. The study used polypropylene mesh in 56% of the patients, PTFE in 40% and polyglactin mesh in 4%.

The chest wall reconstruction must be tightly sutured to the surrounding bony chest wall using heavy non-absorbable sutures. We prefer to insert the mesh inlay to prevent lung herniation. In substantial defects involving four or more ribs, the mesh can be reinforced with a metallic rib strut that is screwed to the periphery of the defect. One or two struts are sufficient to increase the rigidity of the chest wall. The mesh is then suspended to the metallic strut with heavy sutures. Once the chest wall defect is stabilized, well-vascularized soft tissue coverage should be provided to minimize the risk of graft exposure and potential infection.

Different prosthetic materials have been defined for reconstruction to provide good pulmonary function, protect the intrathoracic organs from infection and trauma, and maintain cosmetic integrity. However, they might be rejected, displaced or cause septic complications such as foreign body reaction [19].Although the frequency of wound complications varies between 10-20% in the first 90 days, journals report that 5% of patients require the removal of the prosthesis [22]. In the study, complications developed in 10 patients (20%) and the mesh was removed in 2 patients (4%). Our results were found to be compatible with the literature.

They are generally metallic materials designed to bridge costal and sternal defects. It provides more physiological costal respiratory movements than methyl methacrylate and other patch prostheses. They often must be combined with other mucocutaneous flaps or meshes to wrap the chest wall and isolate the pleural space. As a disadvantage, fracture or displacement can be seen in titanium implants with a frequency of up to 44% [23].

In conclusion, reconstructing extensive chest wall defects with or without thoracic wall resection could be challenging. The reconstruction should be performed by adhering to biomimetic principles, in which anatomy is esteemed, the function is preserved, optimal reconstructive materials are chosen, and a multidisciplinary approach to complex reconstruction is undertaken. After an R0 chest wall resection, first skeletal stability must be established with prosthetic or bioprosthetic meshes or a combination of both. Soft tissue coverage must be achieved using one of multiple available rotational, advancement or free flaps. With the new immediate changes in biodegradable scaffoldings and innovation in surgical techniques, outcomes for extensive chest wall reconstruction are expected to continue to improve.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethics approval

This study was approved by the Ankara Atatürk Sanatoryum Training and Research Hospital institutional Ethics Committee (Number 2710: Approved on May 2023).

Authors' contribution

SH: conceptualized and drafted the article, wrote the paper; NS,LNÜA: drafted the article, collected and analyzed data; PB,GF,SŞEG: revised the final version of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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To cite this article: Gonzales-Peña K, Cubas WS, Villanueva-Zúñiga P. Postpneumonectomy bronchopleural fistula: cohort of patients in a Pevurian National Hospital. Curr Thorac Surg 2023 Sep; 8(3): 136-142. doi: 10.26663/cts.2023.0024. CTSID: 986. Online ahead of print.

Original Article

Postpneumonectomy bronchopleural fistula: cohort of patients in a Pevurian National Hospital

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ABSTRACT

Background: Bronchopleural fistula (BPF) is a complication with a great impact on morbidity, mortality and survival in postoperative pneumonectomy patients. Our study aimed to determine the associated clinical-surgical characteristics of the BPF in a Peruvian cohort of patients with BPF following pneumonectomy

Materials and Methods: Cross-sectional, and retrospective study during January 2015-June 2020 in a Peruvian National Hospital. Medical records and operative reports were reviewed, and all patients over age (>18 years) and with all-cause pneumonectomy were considered. The variables were grouped into pneumonectomies with and without BPF, and the characteristics were grouped as a baseline, clinical-surgical and postoperative.

Results: Among fifty-seven patients who underwent pneumonectomy, 28% presented BPF. The mean age was 38.3 ± 15 years, and 62.5% were male. The main pathologies associated with BPF were post-tuberculosis fibrocavitary sequelae (62.5%), pulmonary hydatidosis (18.8%), and post-surgical cavitary sequelae (12.5%). 81.3% were left BPF (p = 0.342) and 100% were related to postoperative empyema (p < 0.05). The mortality associated with BPF was 6.25%, and in the non-BPF group it was 4.87% (p = 0.098). Characteristics that were statistically associated with the presence of bronchopleural fistula were low predicted forced expiratory volume (FEV1) (56.3% vs. 31.7%; p = 0.046), preoperative empyema (37.5% vs. 2.4%; p = 0.001), postoperative empyema (100% vs. 9.8%; p = 0.000) and operative time (450.69 min vs. 367.73 min; p = 0.032).

Conclusions: There are a series of factors associated with the presence of patients with BPF following pneumonectomy, many of them mainly related to operative and postoperative events, which is an important predictor of associated complications in our Peruvian population.

Keywords: bronchopleural fistula; pneumonectomy; empyema; tuberculosis; complication.

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Doi: 10.26663/cts.2023.0024
Received 08.04.2023 accepted 01.06.2023

Introduction

Bronchopleural fistula (BPF) is a complication with a great impact on morbidity and mortality (6-71%) in post-operative pneumonectomy patients [1-3], and is defined as the communication of a bronchus into the pleural cavity. Many cases are more frequently associated with patients with BPF following pneumonectomy than with other pulmonary resections [4]. It has been reported in 20% of post-operative patients with complete lung resection due to benign etiology (Mycobacterium tuberculosis) and 4.5% in lung cancer [5,6]. The diagnosis of post- pneumonectomy BPF can be early or late and leads to a chronic situation that weakens the patient, leading to malnutrition problems, risk of reactivating tuberculous infections with Multidrug-Resistant germs (MDR), and even leading to death in 10% [1,4,7]. Among the main factors widely described are a history of pulmonary tuberculosis (35%), malnutrition (21%), and right pneumonectomy (15%) [1-3,8-11].

Latin America has with the highest rate of indication of extensive tuberculous pulmonary resections in our environment. This has led to the need to implement operating rooms strictly for this type of surgery such as the one in our institution, with higher rates of BPF than in lung cancer surgeries. Although the surgical technique has progressed, which has generated a decrease in the incidence of BPF, it continues to generate great concern for the thoracic surgeon due to the multifactorial origin of this complication. Therefore, our study aimed to determine the associated clinical-surgical characteristics of the BPF in a Peruvian cohort of patients who underwent pneumonectomy.

Materials and Methods

Design, population, and sample size

A cross-sectional and retrospective study was conducted. Fifty-seven post-pneumonectomy patients previously evaluated by the thoracic surgery service of a Hospital Nacional from Peru during January 2015-June 2020 were studied. Inclusion criteria were the majority of age (>18 years), and pneumonectomy due to different etiologies (tuberculosis, pulmonary hydatidosis, malignant pulmonary tumor, benign pulmonary tumor, severe pulmonary sequelae, and others) and that ended with or without BPF. All patients who underwent pneumonectomy with or without BPF outside the study period and without complete information were excluded.

Data collection and study variables

Data collection was retrospective, and medical records and operative reports were evaluated using a data collection form. Subsequently, the data were tabulated in an orderly manner and respected the chronological order of the patients. A checklist was used, and to avoid any tabulation bias, each of the data obtained was double-checked. The study variables were divided into 2 groups (Pneumonectomies with BPF vs. Pneumonectomies without BPF) and the characteristics evaluated were baseline (age, sex, comorbidities, smoking and alcoholism history), clinical-surgical (pulmonary tuberculosis, type of surgical indication, malnutrition, anemia, hypoalbuminemia, chronic obstructive pulmonary disease (COPD), diabetes mellitus, forced expiratory volume during the first second (FEV1 predicted), overall health (ASA >II), mechanical ventilation greater than 2 hours, pleural empyema pre and post-surgery, pleural empyema pre and post-surgery (pleural empyema pre and post-surgery), mechanical ventilation greater than 24 hours, pre-and postoperative pleural empyema, neoadjuvant therapy and postoperative pulmonary infection, location and type of pneumonectomy, type of suture, operative bronchial closure technique (SWEET, separate loose stitch plication of the cartilaginous bronchial portion over the membranous part, and MABIT, bloc closure of the bronchial stump with arterial and/or venous vessels from the pulmonary hilum), bronchial stump coverage, lymph node dissection, residual tumor in bronchial stump, operative time, intraoperative bleeding and the presence of BPF). The present investigation respected ethical principles, and patient anonymity, and since it was a retrospective study, it was not necessary to implement informed consent. The study protocol was approved by the ethics committee of the Universidad de San Martín de Porres (USMP-00456/2022) and the Hospital Nacional Hipólito Unánue (NIT2309-06/2022), Lima, Peru.

Statistical Analysis

Statistical calculations were based on descriptive analyses with continuous variables (Mean and Standard Deviation) and categorical variables (Counts and percentages). Statistical tests were based on Chi-square, Student's t-test, Fisher's exact test, and the Mann-Whitney U test. The entire statistical analysis of the data was performed with the statistical programs Microsoft Excel 2020 and SPSS v25 for Windows version 10, and values with $p < 0.05$ were considered statistically significant.

Results

Fifty-seven patients who underwent pneumonectomy were evaluated, 28.1% of whom presented BPF. The mean age of the patients with BPF was 38.3 ± 15 years and the male sex prevailed over the female sex (62.5% vs. 37.5%). Twenty-five percent of the patients with BPF had a history of smoking and alcoholism, with no statistically significant relationship (Figure 1).

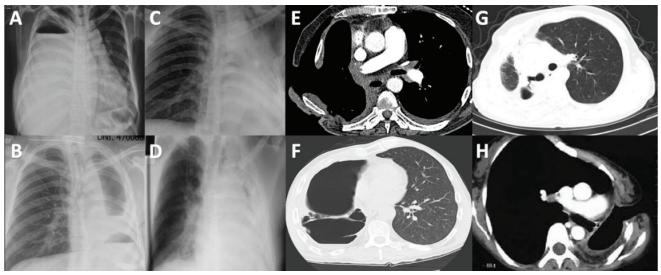

Figure 1. Thoracic radiographs showing various presentations of BPF, including postoperative empyema and collection **(A-D)**, thoracic CT scans show BPF with the presence of postoperative collections and others with thoracic windows **(E-H)**.

About the clinical comparison between the pneumonectomies sample with and without BPF, there was a history of pulmonary tuberculosis in 68.2% vs. 62% (p = 0.225), respectively; however, for patients with BPF, 62.5% had a post-TB fibrocavitary sequela, 18.8% had pulmonary hydatidosis, and 12.5% had a post-surgical cavitary sequela. The mortality associated with BPF was 6.25%, and in the non-BPF group it was 4.87% (p = 0.098). There was malnutrition in 12.5% vs. 2.4% (p = 0.187), both for patients with and without BPF, anemia 51.2% vs.75% (p = 0.225), hypoalbuminemia 31.3% vs. 14.6% (p = 0.260), Diabetes mellitus 18.8% vs. 7.3% (p = 0.335), predicted low FEV1 56.3% vs. 31.7% (p = 0.046), ASA >II 18.8% vs. 9.8% (p = 0.349), mechanical ventilation >24 hours 6.3% vs. 2.4% (p = 0.486), preoperative pleural empyema 37.5% vs. 2.4% (p = 0.01), preoperative neoadjuvant therapy (100% vs. 100%), postoperative pulmonary infection 18.8% vs. 9.8% and postoperative empyema 100% vs. 9.8% (p = 0.00), respectively for both groups (Tables 1,2). The positive bronchial margins for carcinoma with BPF was 12.5%, and in the non-BPF group it was 7.31% (p = 0.012). Regarding the surgical comparison between the pneumonectomies sample with and without BPF, left pneumonectomy predominated in both groups 81.3% vs. 65.9% (p = 0.342), the main suture thread was polypropylene 56.3% vs. 58.5% (p = 0.430), the main bronchial manual closure technique was SWEET 81.3% vs. 97. 6% followed by MABIT 18.8% vs. 2.4% (p = 0.063), for bronchial stump used pleural coverage 56.3% vs. 75.6% (p = 0.199), lymph node dissection 6.3% vs. 2.4% (p = 0.486), emergency surgery 87.5% vs. 82.9% (p = 1.00), operative time 450.69 min. vs. 367.73 min. (p = 0.032) and finally intraoperative bleeding 2220.63 ml. vs. 1579.15 ml. (p = 0.145), respectively for both groups (Tables 1,2).

Table 1. Baseline characteristics of patients who underwent pneumonectomy with and without BF.

Variables	Pneumonectomies N= 57 (100%) **Bronchopleural fistula**		P*
	No (%) N=41	**Yes (%) N=16**	
Age, Mean ± SD	42.00 ± 14.65	38.31 ± 15.00	0.400
Gender			
Male	32 (78%)	10 (62.5%)	0.317
Female	9 (22%)	6 (37.5%)	
Antecedents			
Smoking			
No	37 (90.2%)	9 (56.3%)	0.105
Current	1 (2.4%)	2 (12.5%)	
Former smoker	0 (0%)	2 (12.5%)	
Unknown	3 (7.3%)	3 (18.8%)	
Alcoholism			
Yes	1 (2.4%)	4 (25%)	0.08
No	37 (90.2%)	9 (56.3%)	
Unknown	3 (7.3%)	3 (18.8%)	
Pulmonary tuberculosis (TB)			
Sensitive	23 (56.1%)	5 (31.3%)	0.225
MDR	7 (17.1%)	5 (31.3%)	
Pulmonary disease			
Fibrocavitary sequelae post-TB	29 (70.7%)	10 (62.5%)	
Hydatidosis	6 (14.6%)	3 (18.8%)	
Neoplasia	2 (4.9%)	1 (6.3%)	0.848
Bullous lung	1 (2.4%)	0 (0%)	
Post-resection residual cavity	1 (2.4%)	0 (0%)	
Malnutrition	1 (2.4%)	2 (12.5%)	0.187
Anemia	21 (51.2%)	12 (75%)	0.342
Hypoalbuminemia	6 (14.6%)	5 (31.3%)	0.260
COPD	0	1 (6.3%)	0.281
Diabetes Mellitus	3 (7.3%)	3 (18.8%)	0.335

*Abbrev.; SD: Standard Deviation, COPD: Chronic obstructive pulmonary disease, MDR: Multidrug-Resistant, *Student's t-test*

Table 2. Clinical-surgical characteristics of patients who underwent pneumonectomy with and without BF.

Variables	Pneumonectomies N= 57 (100%)		P
	Bronchopleural fistula		
	No (%) N=41	Yes (%) N=16	
Pneumonectomy			
Right	14 (34.1%)	3 (18.8%)	0.342
Left	27 (65.9%)	13 (81.3%)	
Suture thread			
Black Silk	12 (29.3%)	3 (18.8%)	0.430
Polypropylene	24 (58.5%)	9 (56.3%)	
Vicryl	5 (12.2%)	4 (25%)	
Manual bronchial closure technique			
Sweet	40 (97.6%)	13 (81.3%)	0.063
Mabit	1 (2.4%)	3 (18.8%)	
Positive bronchial margins for carcinoma	3 (7.31%)	2 (12.5%)	0.012
Bronchial stump coverage			
Intercostal muscle flap	1 (2.4%)	2 (12.5%)	0.199
Pleural	31 (75.6%)	9 (56.3%)	
Lymph node dissection	1 (2.4%)	1 (6.3%)	0.486
Emergency surgery	7 (17.1%)	2 (12.5%)	1.000
Operative time (Minutes)	367.73 ± 112.76	450.69 ± 169.36	**0.032**
Intraoperative bleeding (mL)	1579.15 ± 816.85	2220.63 ± 1456.72	0.145
Predicted low FEV1	13 (31.7%)	9 (56.3%)	**0.046**
ASA >II	4 (9.8%)	3 (18.8%)	0.349
Mechanical ventilation >24 hours	1 (2.4%)	1 (6.3%)	0.486
Preoperative pleural empyema	1 (2.4%)	6 (37.5%)	**0.001**
Preoperative antibiotic therapy	41 (100.0%)	16 (100.0%)	**NC**
Postoperative pulmonary infection	4 (9.8%)	3 (18.8%)	0.388
Postoperative empyema	4 (9.8%)	16 (100%)	**0.000**
Mortality	2 (4.87%)	1 (6.25%)	0.098

Abbrev.; NC: Not calculated, FEV1: Forced expiratory volume during the first second, ASA: American Society of Anesthesiologists

Discussion

BPF is a complication that represents 59% of morbidity and 5.4-71% of mortality in patients who underwent pneumonectomy [1-3]. Our research reported an incidence of 28.1% of BPF, with a higher percentage reported in studies by Mammana (4.5%), Gursoy (10.8%), and La Serna (11%) [6,12,13]. We described a history of sequelae of TB infection in 68.4%; however, several authors have reported higher rates exceeding 75% [10,12,14,15]. This could be explained by the fact that chronic inflammation due to tuberculosis leads to the deposition of collagen at the hilar level and stiffer anatomical structures; consequently, bronchial tissue is predisposed to impaired healing and a greater risk of BPF [6]. BPF was found to be mainly associated with the male gender (62.5%); being similar to that reported by La Serna, who described that 69% of the population was male [13]. Mammana et al suggested that a possible explanation could be that the diameter of the male bronchus is larger and when closing the bronchial stump this would generate greater tension; on the other hand, Nachira et al reported that the female sex was an associated factor for post-pneumonectomy BPF (p = 0.03) [3,6]. The mean age of patients with BPF reported in our study (38.31 ± 15 years) was somewhat different from that reported by Fuso and Ahmet et al as they described 66.1 ± 7.4 years and the latter would be due to the etiology associated with BPF such as neoplasms, unlike our case, mainly young population and with infectious etiologies [9,10,16].

We identified a statistically significant association (p = 0.015) between smoking and BPF, similar to that reported by Thomas et al and describing that active smoking was a significant predictor of BPF (OR 1.6; 95%CI, 1.34-1.95, p = 0.017) [11]; however, Yazgan and Mazzela et al did not find a clear significant association [8,10]. Likewise, alcoholism was significantly associated with BPF (p= 0.008), similar to that described by Thomas et al (OR 2.2; 95%CI, 1.98-2.45, p = 0.017), describing alcohol abuse and dependence as a negative predictor for BPF [11]. In Peru, the main indication for pulmonary surgery is for sequelae pulmonary TB, and we report more than 50% incidence of pulmonary TB for both groups; however, without statistically significant association with BPF [14]. Mammana et al also reported no significant association in 20% of their cases [6]; but Gursoy and Ahmet et al reported that 33.3% of patients with pulmonary TB were associated with the presence of post-pneumonectomy BPF (p = 0.08) [12, 15].

Among the predictors of BPF development described by Pforr et al the presence of non-malignant pulmonary disease (p = 0.03) [10] and among which pulmonary sequelae disease (78%) and hydatidosis (34%), were also described by Birdas, and Ahmet et al [15, 17]. Factors such as malnutrition, underweight, anemia, and hypoalbuminemia have been widely related to BPF and were described by Thomas, Pforr, Haraguchi, and Mazzella et al. However,

the latter highlighted that hypoalbuminemia was present in more than 20% of patients affected by BPF ($p = 0.02$) [8,10,11,18]. COPD and low FEV1 predicted postpneumonectomy have been related to the incidence of BPF, because chronic inflammation of the bronchial mucosa in these patients may contribute to impair healing after lung resection [2]. Algar et al described that low postoperative FEV1 is a predictive factor for postpneumonectomy BPF ($p = 0.012$); however, Yazgan and Thomas et al reported that there is no relationship and that more evidence is needed to accept this [2,11,19]. Nachira ($p < 0.019$) and Mammana et al ($p < 0.001$), reported that prolonged mechanical ventilation causes a higher risk of suture tension and has been associated with the presence of BPF [3,6]; however, we do not report a significant association in this item but we do describe that preoperative empyema is strongly associated with this complication and was described by Haraguchi ($p = 0.002$), stating that preoperative pulmonary infections contribute significantly to BPF in postoperative pneumonectomy patients ($p = 0.002$) [19], stating that preoperative pulmonary infections contribute significantly to BPF in postoperative pneumonectomy patients [19]. We did not find an association between BPF and postoperative pulmonary infection as did Fuso et al [9]. However, Nachira et al concluded that postoperative pulmonary infections were strong predictors of BPF development ($p = 0.008$) [3]. Despite this, it has been described that a mechanism of production of BPF is the infection of the pleural space and the increasing accumulation of infected fluid, resulting in the evacuation of empyema through the bronchial stump and subsequent complication into BPF [20]. That is why we report that 100% of the patients who presented BPF had postoperative pleural empyema ($p = 0.000$), similar to what was described by Nachira et al, who reported that postoperative empyema increases the risk of having BPF by 8 times ($p < 0.001$) [3] and also Somocurcio et al concluded that postoperative complications in patients who underwent surgery for multidrug-resistant pulmonary TB were postoperative empyema followed by BPF [13]. The greater frequency of BPF in right pneumonectomy is due to its blood vascularization which is nourished by one artery, compared to the left bronchus which is perfused by two bronchial arteries; likewise, another protective mechanism would be that in left pneumonectomy, the bronchial stump is covered by the aorta and surrounding tissues [2,18]. All the above described has been reflected in publications by Mammana (OR 4.08; 95%CI, 3.67-4.67, $p = 0.004$), Gursoy (OR 5.90; 95%CI, 4.97-6.32, $p = 0.001$) and Mazzella et al (OR 2.53; 95%CI, 2.11-3.35, $p = 0.023$), concluding that right pneumonectomy is an associated factor for the development of BPF [6,8,12]. One of the possible causes of BPF is the use of inadequate suture material. Non-absorbable thread (stainless steel, silk, polypropylene) gives better results, the other types are eliminated with the risk of BPF [21]. In the present study; only suture thread was used for bronchial stump closure, no mechanical sutures were used. The most frequent thread used in patients with BPF was polypropylene (56.3%) but no significant association was found. Gursoy et al reported that of the cohort of patients with BPF, automatic suture (74.5%) and manual suture (polypropylene, 25.5%) were used but without significant differences [12]; however, Mammana et al described that the use of vicryl was one of the factors that showed a significant positive trend over time towards BPF ($p < 0.001$) [6]. Ahmet et al reported that of the mechanical and manual suture group (polypropylene), 5% and 1.5% respectively, developed BPF, and it was concluded that mechanical suture was associated with BPF ($p = 0.04$) [15]. The bronchus closure technique with continuous stitches (Mabit Technique) was performed in intraoperative complications such as bleeding, which required quick control of the pulmonary hilum, in sequelae lung, chronic empyema, and in case of previous pulmonary resection, where it was very difficult to separate vascular structures and bronchus. With this technique, 75% BPF was described, in contrast to the sweet technique with 32.5%. This factor was evaluated because, with continuous suturing, one of the basic principles of bronchial stump closure would be affected, that of conserving the blood supply and thus affecting the irrigation of the bronchial stump [1]. In the literature, manual and mechanical closure techniques are compared, and their use in bronchial stump closure is still controversial [3,6,9].

Lymph node dissection in pneumonectomy, especially in right pneumonectomy, has been associated with greater devascularization of the bronchial stump, causing greater vascular damage of the nutrient vessel in surgery and being a risk factor for the presence of BPF [2,18], we did not report a significant association due to the few cases; neither was it described in other studies such as those of Pforr, and Thomas et al [10,11]. Mammana et al reported that residual tumor in the bronchial stump is a risk factor for post-pneumonectomy BPF ($p = 0.018$); however, we did not find any association in the sample studied [6]. La Serna described that the distorted anatomy of patients with sequelae of pulmonary tuberculosis would cause greater intraoperative complications since

pulmonary dissections are difficult and increase the operative time [13]. We described a longer operative time in patients who underwent pneumonectomy and BPF than those who did not present this complication, being a significant and related finding ($p = 0.032$); likewise, Thomas et al also concluded that increased operative time is an associated predictor factor for BPF [11].

Among the limitations of our study was the small sample size of our population; however, despite being one of the leading institutions in the surgical management of TB, we have a small caseload. We also believe that a longer-term follow-up study would be ideal for this group of patients with BPF who underwent pneumonectomy

In conclusion, we have found a series of factors associated with the presence of BPF in patients who underwent pneumonectomy, many of them related to pulmonary tuberculosis infection, which is an important predictor of the associated complications; however, we believe that further multicenter studies with a larger number of patients are needed to identify more factors to be considered during the surgical management of this terrible complication such as BPF.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethics approval

The study protocol was approved by the ethics committee of the Universidad de San Martín de Porres (USMP-00456/2022) and the Hospital Nacional Hipólito Unánue (NIT2309-06/2022), Lima, Peru.

Authors' contribution

KGP, WSC: Concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review, PVZ: Data acquisition, data analysis, manuscript editing and manuscript review.

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To cite this article: Utkusavas A, Akkus M, Kolbas I, Ikitimur H. Pathological diagnoses and adenosine deaminase levels in patients undergoing pericardial window operation for large pericardial effusions. Curr Thorac Surg 2023 Nov; 8(3): 143-147. doi: 10.26663/cts.2023.0025. CTSID: 964. Online ahead of print.

Original Article

Pathological diagnoses and adenosine deaminase levels in patients undergoing pericardial window operation for large pericardial effusions

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ABSTRACT

Background: It might be challenging to determine the etiology of pericardial effusions as studies have usually focused on pericardial effusions in patients suspected to have specific underlying clinical conditions. We aimed to evaluate adenosine deaminase (ADA) levels in pericardial fluid samples of patients with large pericardial effusions in whom pericardial window surgeries with biopsy and pathological examinations were carried out.

Materials and Methods: Pericardial fluid ADA levels of 149 consecutive patients having large pericardial effusions were evaluated. Pericardial effusion was detected by transthoracic echocardiography, ADA levels were measured from the fluid taken during pericardial windowing procedure, and pathological examination of the tissue samples were performed.

Results: The median age of selected patients participating in the study was 58.43 ± 14.47 years. All the pericardial fluid samples were found to be exudative and 116 (77.9 %) of the cases had also concomitant pleural effusions. The median ADA level of the cases was calculated to be 19.57 U/L (9.47-38.70), well below the cut-off value (40 U/L). The mean ADA levels value was 9.21 U/L (7.70-9.91) in the nonspecific inflammations group and 38.35 U/L (23.92-48.67) in the lung malignancy group ($p < 0.001$). In the subgroup analysis of lung cancers, ADA levels in pericardial effusions of patients with adenocarcinoma were found to be statistically significantly higher than patients with squamous cell cancer. ($p = 0.007$).

Conclusion: ADA levels in pericardial effusion were found to be significantly higher in lung cancer, especially in cases of lung adenocarcinoma. High levels of ADA may be used as a significative biochemical marker in the diagnosis of lung cancer.

Keywords: pericardial effusion, adenosine deaminase, cancer

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Doi: 10.26663/cts.2023.0025
Received 24.01.2023 accepted 24.04.2023

Introduction

The pericardial cavity normally contains 10 to 50 mL of serous plasma ultrafiltrate. Accumulation of transudative or exudative fluid of more than least >50 mL is considered abnormal and may lead to significant hemodynamic effects which results in cardiac compression and impaired cardiac filling [1]. While some known underlying diseases like acute myocardial infarction, cardiac surgery, end-stage renal disease, or widespread metastatic neoplasm are the common causes for pericardial effusions, sometimes no obvious cause is apparent. [2,3].

Plasma adenosine deaminase (ADA) level is known to increase to a certain level in several disease states associated with lymphocytic pericardial effusions including neoplasms and some acute viral infections, the most widely known increase is observed in tuberculosis [4].

Routine measurements on pericardial fluid should include white blood cell count and differential cellular analysis, hematocrit, and glucose and protein content. Pericardial fluid should be routinely stained and cultured for bacteria, including Mycobacterium tuberculosis and fungi. If there is any suspicion of tuberculous pericarditis, testing for adenosine deaminase and/or polymerase chain reaction should be a routine procedure since waiting for pericardial fluid culture results can markedly delay the diagnosis [3].

Our study aimed to compare the cytological results and pericardial ADA levels of differently diagnosed patient groups, undergoing pericardial fenestration because of consecutive large pericardial effusions that are clinically indicated in a third-level hospital.

Materials and Methods

This study is a retrospective observational study. It was carried out in the chest diseases department of a tertiary teaching and research hospital following the approval of the local ethics committee (No: 2019-36).

149 patients, 60 of whom were women, having large pericardial effusions detected by transthoracic echocardiography, despite empirical treatment, were included in the study. Informed consent forms were obtained from all patients before the intervention. Afterward, a video thoracoscopic pericardial window surgery was performed for diagnosis and treatment. After video thoracoscopic visualization, the pericardium was incised over the phrenic nerve, and pericardial fluid was aspirated with an aspirator. 20 mL of the liquid was taken to evaluate ADA activity. The pericardium was incised, the area was enlarged and an average of 4x4 cm pericardium was resected with ultrasonic scissors and separated as a pathological sample. During the procedure, pericardial fluid was sampled and adenosine deaminase (ADA), albumin and lactate dehydrogenase (LDH) levels were measured. The demographic characteristics of the patients are demonstrated in table 1.

Transthoracic echocardiography

2-D transthoracic echocardiography (TTE) is the imaging modality of choice for the evaluation of pericardial effusion as well as tamponade physiology. TTE should also be used to guide pericardiocentesis. Pericardial effusions appear as an echolucent space between the parietal and visceral pericardium. Pericardial effusions are graded as small (echo-free space in diastole <10 mm), moderate (10–20 mm space), and large (more than 20 mm space) [5].

Exudative-transudative effusions

Useful criteria in favor of exudative pericardial effusions include a pericardial fluid to serum protein ratio greater than or equal to 0.5 and/or pericardial fluid to serum LDH ratio greater than or equal to 0.6 and/or pericardial fluid lactate dehydrogenase value greater than or equal to 200 U/L [6].

ADA analyses

The Giusti technique for measuring ADA activity through calorimetry was uniformly used in all the selected studies. ADA was determined in the same samples following Giusti's method [7] by simultaneously taking blood and pericardial fluid samples, centrifuging them for 3 h, and freezing the remainder at –20°C. For each patient ADA levels (U/L) were determined in the pericardial fluid (the cut-off value for increased ADA level was 40 U/L) [8].

Statistical Analysis

SPSS 26 (IBM Corp, 2019, IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY) was used to process the data obtained in the study. The conformity of the data to the normal distribution was evaluated with histograms, Q-Q plots, and the Shapiro-Wilk test. Continuous data conforming to the normal distribution is expressed as the mean and standard deviation, non-conforming data is expressed as the median and percentiles of 25% - 75%, and nominal variables are expressed as frequency and percentage. An intergroup comparison T-test or Mann-Whitney U test was performed according to the normal distribution The Chi-square and, where necessary, Fisher's Exact tests were used to compare

nominal variables. The statistical significance level was accepted as $p < 0.05$ for all calculations.

Results

The median age of patients participating in the study was 58.43 ± 14.47 years (Table 1). All the pericardial fluid samples were found to be exudative and 116 (77.9 %) of the cases had also concomitant pleural effusions.

Pathological diagnoses were as follows: 60 nonspecific inflammations, 59 lung cancer metastasis, 14 pericarditis, 7 granulomatous inflammations, 4 breast cancer metastasis, 3 renal cell cancer metastasis and 2 mesotheliomas (Table 2). The median ADA levels of the cases was calculated to be 19.57 U/L (9.47 - 38.70), well below the cut-off value (40 U/L) (Table 3).

As the number of patients was low in the pathological diagnosis subtitles except lung cancer metastasis and nonspecific inflammation group, a statistical study was performed between these two groups (Table 4). The mean ADA level was 9.21 U/L (7.70 - 9.91) in the nonspecific inflammations group and 38.35 U/L (23.92 - 48.67) in the lung malignancy group ($p < 0.001$). In the subgroup analysis of lung cancers, ADA levels in pericardial effusions of patients with adenocarcinoma were found to be statistically significantly higher than in patients with squamous cell cancer. ($p = 0.007$) (Table 5).

Table 1. Demographic characteristics of the patients with pericardial effusion.

(n=149)	N(%) Mean±SD Median (%25-75)
Age	58.43±14.47
Female	60(40.3)
Male	89(59.7)

Table 2. Pathological diagnoses of the patients with pericardial effusion

Nonspecific inflammations	60(40.3)
Lung malignancy	59(39.6)
Pericarditis	14(9.4)
Granulomatosis inflammations	7(4.7)
Brest cancer	4(2.7)
Renal cell cancer	3(2)
Mesothelioma	2(1.3)

Table 3. Laboratory results of the patients with pericardial effusion.

ADA	19.57 (9.47-38.70)
Total Protein	4.84 (4.11-5.44)
Albumin	2.913±0.657
LDH	532 (305-740)

Discussion

Pericardial effusion is a common cardiovascular disease that occurs due to benign or malignant causes [9]. Pericardial effusion with a transudate nature is mainly caused by systemic diseases such as cardiac, kidney and liver disease, or endocrine disorders such as hypothyroidism. Pericardial effusions of an exudate nature are usually because of malignancy or tuberculosis [9]. Treatment strategies for pericardial effusion depend on etiology and prognosis. Therefore, the diagnosis should be made quickly and accurately.

Survival in patients with malignant pericardial effusion is usually less than 12 months, and hemodynamic instability and death due to pericardial tamponade develop in 1/3 of malignant patients [10].

The clinical manifestations of patients with malign pericardial effusion are not specific, and it can be quite difficult to distinguish malignant pericardial effusion from benign pericardial effusion. Though exfoliative cytology and diagnostic pericardial biopsy of pericardial effusion are of decisive importance in the diagnosis of malignant pericardial effusion, the sensitivity of these methods is relatively low [10]. The accuracy of cytological fluid analysis is 67-92% and negative reporting of cytology does not exclude malignancy [10-12].

Because of pericardial fluid sampling is a difficult procedure, there are limited resources and studies on this tissue [10]. In this context, proof can be obtained by using biochemical biomarkers that can give results faster than the pathological examination [13-15].

Imazio et al reported that pericardial effusions are found to be idiopathic in many cases in developed countries whereas tuberculosis is the leading cause of pericardial effusions in developing countries where it is endemic [16].

Porte et al studied 114 patients with a recent or remote history of cancer and pericardial effusion of unknown origin for which drainage was required for diagnostic or therapeutic purposes [17]. The malignant pericardial disease was found in 44 (38%) patients, while 70 (61%) patients had non-malignant pericardial effusions (idiopathic in 33 patients, radiation-induced in 20 patients, infectious effusion in 10 patients, and hemopericardium as a result of coagulation disorders in 8 patients) [17].

Table 4. The analysis of primary outcome.

(n=119)	Inflammation n (%) 60 (50.4)	Malignancy n (%) 59 (49.6)	OR (%95 GA)	p
Age Mean±SD	59.2±14.9	60.8±13.1	-	0.525
Sex (female) n (%)	25(41.7)	22(37.3)	-	0.625
ADA	9.21(7.70-9.91)	38.35(23.92-48.67)	-	<0.001
Total Protein	5.14(4.17-5.53)	4.61(3.99-5.09)	-	0.01
Albumin	2.99±0.66	2.71±0.64	-	0.022
LDH	581(303-872)	639(305-762)	-	0.722
Pleural effusion n (%)	43(71.7)	50(84.7)	-	0.084

Table 5. The analysis of secondary outcome.

(n=59)	Squamous cell ca n (%) 27 (45.8)	Adenocarcinoma n (%) 32 (54.2)	OR (%95 GA)	P
Age. Mean ± SD	60.2±13	61.4±13.5	-	0.719
Sex (Female). n (%)	7 (25.9)	15 (46.9)		0.097
Laboratory results Mean ± SD / Median (%25 - %75)				
ADA	29.97 (20.18-44.49)	44.63 (35.98-50.83)	-	0.007
Total Protein	4.55±0.94	4.41±1.12	-	0.633
Albumin	2.64±0.65	2.76±0.64	-	0.476
LDH	646 (392-782)	567 (235-709)	-	0.267
Pleural effusion* n (%)	22 (81.5)	28 (87.5)	-	0.719

** The p value was found by Fisher's exact test.*

The study by Sagristà- Sauleda et al [3], included 322 patients, 132 with moderate and 190 with severe pericardial effusion. In this series, the most common diagnosis was acute idiopathic pericarditis which accounted for 20% of patients. The next most prevalent diagnoses were iatrogenic effusion (16%), neoplastic effusion (13%), and chronic idiopathic pericardial effusion (9%) [3]. Lui et al, in their study including 110 cases, showed that there was no significant difference in ADA levels as 37.63 ±31.98, 38.21 ± 94.45 of patients having a diagnosis of tuberculosis and malignant pericardial effusion.

Malignant pericardial effusion is the most common presentation of tumoral infiltration of the pericardium and may sometimes be the first symptom of a malignant disease which is detected in approximately 40-50% of patients with severe pericardial effusion [18,19].

ADA is an enzyme required for the conversion of adenosine to inosine. ADA can be found in all tissues, but the largest concentration is in the lymphoid tissue, mainly in T-lymphocytes [20].

As in line with the literature, in our study, the mean pericardial fluid ADA levels were not found to be increased in patients having large pericardial effusions caused by malignancy and non-specific inflammation. Aggeli et al reported that ADA levels were found to be high in the group consisting of 2 lung and 2 breast cancer patients. In the same literature, ADA levels were found to be low in 10 cases with pericardial effusion due to idiopathic causes [21].

Increased ADA levels due to malignant effusions have been reported in clinical studies [2,22]. When the cause of ADA increase in malignant pleural etiologies was evaluated, it was shown that it was associated with the increase in cytokines related to inflammation (due to increased levels of interleukin 8) and permeability (vascular endothelial growth factor, transforming growth factor B) [22]. In these studies, the cause of malignant pleural effusions was lung cancer but the pathological subtype was not determined. In our study, we found that the ADA levels in pericardial effusions caused by lung cancer is significantly higher in the adenocarcinoma subtype.

In conclusion, ADA levels in pericardial effusion were found to be significantly higher in lung cancer, especially in cases of lung adenocarcinoma. High levels of ADA may be used as a significative biochemical marker in the diagnosis of lung cancer.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethics approval

The study was approved by the Local Ethics Committee of University of Health Sciences, Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital. The committee's reference number is a (2019/36).

Authors' contributions

AU; conceptualized and drafted the article, wrote the paper MA,IK; drafted the article, collected and analyzed data, HI; collected data.

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To cite this article: Gürsoy D, Samancılar Ö, Turhan K. Video-assisted thoracoscopic surgery lobectomy with guillotine stapler technique for the second primary adenocarcinoma of the lung after immunotherapy. Curr Thorac Surg 2023; 8(3): 148-150.

Case Report

Video-assisted thoracoscopic surgery lobectomy with guillotine stapler technique for the second primary adenocarcinoma of the lung after immunotherapy

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ABSTRACT

Immunotherapy is gaining increasing attention as a neoadjuvant therapy for resectable non-small cell lung cancer (NSCLC). We report a case with second primary lung adenocarcinoma that was applied via video-assisted thoracoscopic surgery (VATS) lobectomy with guillotine stapler technique after treatment with immunotherapy in combination with chemotherapy. Although surgery is challenging after immunotherapy, this particular case showed that the VATS approach may be safe and feasible in experienced hands.

Keywords: non-small cell lung cancer, neoadjuvant therapy, immunotherapy, video-assisted thoracoscopic surgery (VATS), nivolumab, lung resection

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Doi: 10.26663/cts.2023.0026
Received 21.12.2022 accepted 28.03.2023

Introduction

Immunotherapy has achieved great success in treating lung cancer. Three major immunotherapy treatment modalities mentioned in the literature are immunomodulatory antibodies, chimeric antigen receptors (CARs) and vaccines [1]. Immune checkpoint inhibitors (ICIs) for advanced lung cancer are gaining increasing attention as a neoadjuvant therapy for resectable non-small cell lung cancer (NSCLC). Meanwhile, data regarding the safety and feasibility of surgical resection after treatment with immunotherapy for NSCLC remains scarce.

We report a case with second primary lung adenocarcinoma who was operated via video-assisted thoracoscopic surgery (VATS) lobectomy with guillotine stapler technique after treatment with immunotherapy in combination with chemotherapy.

Case Report

A 61-year-old female patient admitted to our hospital in 2014 with complaints of hip pain, cough and shortness of breath. Computed tomography images revealed lytic bone metastasis in the left acetabulum and a mass invading the mediastinum in the upper lobe of the right lung. On PET imaging, a mass of 3.5 cm in size, showing 15.6 FDG uptake, invading the mediastinum narrowing the right upper lobe bronchus, multiple mediastinal hypermetabolic lymphadenopathy and left iliac bone metastasis were observed. The patient was diagnosed as stage IV lung adenocarcinoma after a bronchoscopic biopsy. She had severe pain following radiotherapy and zoledronic acid treatment for acetabular bone metastasis, and she was operated on for hip arthroplasty. Postoperative bone pathology was reported as metastatic adenocarcinoma of the lung. After 3 cycles of carboplatin and pemetrexed chemotherapy, three cycles of docetaxel chemotherapy was given due to the progression of the lung mass. Nivolumab immunotherapy, a PD-1 blocking agent, which is one of the checkpoint inhibitors, was started for the patient whose tumor size continued to increase. In the imaging after 10 cycles of treatment, the tumor in the upper lobe of the right lung was observed to regress almost completely. In the CT scan of the patient in the year 2022, after eight years from the first diagnosis with the complaint of cough and three years since the last nivolumab dose usage, a 20x13 mm spiculated nodule at the right lung lower lobe was observed (Figure 1). The SUVmax value of the nodule was 9.2 on PET-CT and no metastasis was detected on the remaining body parts. The Patient was prepared for VATS lobectomy. Pathological result by frozen section confirmed NSCLC. On exploration, there were very dense pleural adhesions and severe tissue fibrosis on the hilum thought to be due to immuno-chemotherapy causing a very difficult and dangerous dissection. After division of the inferior pulmonary vein, the lower lobe artery and lower lobe bronchus, which were "fusioned" were dissected and divided together with an endostapler using the "guillotine stapler technique"[2]. The middle lobe bronchus was protected by transillumination of the fiber optic bronchoscope delivered through the endobronchial tube from the surgical field. Lymph node dissection was difficult due to mediastinal rigidity. After the surgical procedure, the patient had an uneventful recovery and was discharged from the hospital on the fifth postoperative day. The pathological diagnosis was secondary primary lung adenocarcinoma (T1cN0M0, Stage IA3). Written informed consent was obtained from the patient for the publication of her data.

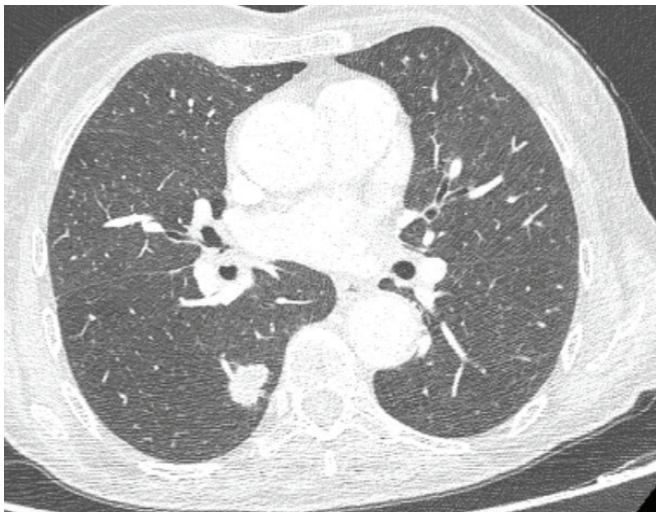

Figure 1. A spiculated nodule at the right lower lobe was observed 8 years after the first diagnosis.

Discussion

There are several advantages of neoadjuvant therapy, e.g., increasing the resectability by downstaging the lung tumors, improving the rate of lung sparing surgery, and increasing distant and local disease control [3]. Immune checkpoint inhibitors (ICIs) such as atezolizumab, durvalumab, nivolumab, and pembrolizumab have been approved for first- or second-line use in patients with metastatic NSCLC or selected stage III locally advanced NSCLC. Neoadjuvant ICIs are currently being evaluated alone or in combination with chemotherapy in many clinical trials in patients with diverse tumor types [4]. However, the risks of disease progression before surgery, delays to resection, perioperative morbidity and mortality, and their impact on intraoperative technical difficulty after neoadjuvant ICIs are still poorly understood. Although the therapeutic value of resecting residual primary or metastatic foci remains controversial in general, the safety and feasibility of pulmonary resection after treatment with immunotherapy agents, in particular, have

not yet been studied. Benign lung diseases, secondary infections, malignancy itself, chemotherapy, radiation and immunotherapy as a neoadjuvant therapy can usually be accompanied by inflammation as a result, peribronchial conglomerated lymph nodes, adhesions and fusion between the artery and bronchus, and hypertrophy of the bronchial arteries may occur [2]. In these cases, there is a high risk of complications, such as bleeding during hilum dissection. In our case, very dense adhesion between the artery and bronchus and the rigid connective tissue were the challenging parts of the surgery which led us to choose the guillotine technique. Minimally invasive approaches are feasible in this patient population, but may be more difficult than in cases without neoadjuvant immunotherapy. Operations may be challenging, owing to post-treatment adhesions and the surgeon has to be aware and converting to open thoracotomy may be necessary. Resection after neoadjuvant ICI may increase intraoperative technical difficulty because of inflammation-induced perihilar or lobar dense fibrosis and lymphadenopathy. Due to these difficulties conversion rates of up to 54% have been reported in the literature. The optimal timing of surgery after neoadjuvant immunotherapy is undetermined but most studies scheduled resection approximately 3 to 6 weeks after treatment [5].

In conclusion we reported a case of right lower lobectomy due to second primary lung adenocarcinoma in a patient who received long term immunotherapy after her first primary. Although surgery is challenging after immunotherapy, this particular case showed that the VATS approach may be safe and feasible in experienced hands. The use of the guillotine technique may be necessary for patients having strong adhesions between pulmonary artery and bronchus to avoid injury to vascular structures and bleeding. By cutting the artery-bronchus complex, transillumination of the fiberoptic bronchoscope should be used to check that the middle lobe bronchus on the right side and the upper lobe bronchus on the left side are not obliterated. There is insufficient information about the long-term fistula risk of the guillotine technique in the literature. Therefore, this technique should be applied carefully with the results in mind.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support.

Authors' contributions

DG,ÖS,KT: conceived and designed the current case report, co-wrote the paper, collected the clinical data. The authors discussed the case under the literature data together and constituted the final manuscript.

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Current Thoracic Surgery

To cite this article: Valderrama-Saldaña M, Cubas WS, Reina H, Somocursio J, Small M. Pulmonary carcinoid tumor of endobronchial presentation: a case report. Curr Thorac Surg 2023; 8(3): 151-154.

Case Report

Pulmonary carcinoid tumor of endobronchial presentation: a case report

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ABSTRACT

Lung carcinoid tumors account for 1-2% of malignant lung neoplasms. Early diagnosis is crucial, and surgery at an early stage may improve the clinical picture and may even be a curative option. We present a 78-year-old woman with a history of poorly controlled arterial hypertension, anxious syndrome, irritable bowel syndrome, and paroxysmal palpitations for the last two years. Radiologic imaging showed a left hilar nodular lesion causing endobronchial obstruction in the left lower lobe. Anatomopathology revealed a low-grade pulmonary neuroendocrine tumor, and pulmonary resection with nodal staging was promptly considered. The diagnosis of pulmonary carcinoid tumor is challenging; therefore, it is necessary to maintain suspicion in patients with non-specific and/or persistent respiratory symptoms, and complete resection and prolonged close follow-up should be considered despite a satisfactory postoperative course.

Keywords: carcinoid tumor, neuroendocrine tumor, lung tumor, carcinoid syndrome

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Doi: 10.26663/cts.2023.0027
Received 13.02.2022 accepted 13.06.2023

Introduction

Pulmonary carcinoid tumors are a group of neuroendocrine tumors originating from Kulchitsky neuroendocrine cells [1] and account for 1-2% of malignant lung neoplasms, with an incidence of 1.49/1,000,000 population [2]. They occur in all age groups with a peak incidence around the fifth decade. The clinical presentation is silent in up to 25-39% of cases, being diagnosed with non-specific symptoms, or with cough (15%), hemoptysis (24%), dyspnea (22%), recurrent pneumonia, atelectasis (7%), and rarely as carcinoid syndrome (8%) [3]. They are classified into typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNC)/small cell lung carcinoma (SCLC) (1), considered analogous to grade 1, 2, and 3 neuroendocrine tumors of other locations respectively, being according to the mitotic index and necrosis present in typical (< 2 mitoses/2 mm2 with the absence of necrosis and more than 0.5 cm) and atypical (2-10 mitoses/mm2 or necrosis often punctate). Diagnosis is based on imaging studies to identify the presence of hilar involvement, endobronchial tumors, signs of bronchial obstruction, mediastinal lymph node involvement, and pulmonary nodules. Some reviews have described that the main location is at the segmental or subsegmental bronchi level (80%), and others mention that up to 75% of cases present endobronchial lesions [4]. This latter presentation makes the use of flexible bronchoscopic techniques necessary as the best method for the anatomopathological study. Surgery is the main treatment of choice, and surgical indication at an early stage can mean clinical improvement and even a definitive curative option, especially in typical carcinoma, which is why it is important to know about this entity.

Case Report

A 78-year-old woman with a history of uncontrolled arterial hypertension, irritable bowel syndrome, anxiety syndrome, and paroxysmal palpitations for two years. She received symptomatic medical treatment and with the passage of time, liquid stools, abdominal pain, and persistent precordial pain were added, for which reason she went for medical consultation. A sinus tachycardia with supraventricular extrasystoles was identified and a chest X-ray showed a nodular image in the left para-retrocardiac region. The tomographic study showed a left lesion of 3x3 cm, of solid characteristics with involvement of the left lower lobe bronchus (LLB), and due to the high suspicion of malignancy, she underwent a bronchoscopic study (Figure 1). This last evaluation reported a friable endobronchial lesion at the level of the LII entry that caused an occlusion of 90% of the bronchial lumen, and finally, the anatomopathological study revealed small cellular nests with organoid patterns with characteristics suggestive of the neuroendocrine lesion at the bronchial wall level. Immunohistochemistry was compatible with a low-grade (Grade I) pulmonary neuroendocrine tumor in bronchial mucosa TTF-1: (Negative), Chromogranin: (+++), CK20: (Negative), PanCK: (+), Ki67: (2%). After diagnostic confirmation, the tumor was resected, which was included next to the left lower lobe, and the corresponding lymph node resection was performed. The study of the operative specimen also showed involvement of the submucosa and part of the bronchial cartilage, with a mitotic index (< 1%) and Ki67 index: (4%) (Figure 2). The patient had an optimal postoperative recovery and was discharged with the indication for periodic outpatient follow-up. After nine months, no signs of recurrence have been observed and the patient has shown significant clinical improvement, with no additional medication and good functional class. Written informed consent was obtained from the patient for the publication of her data.

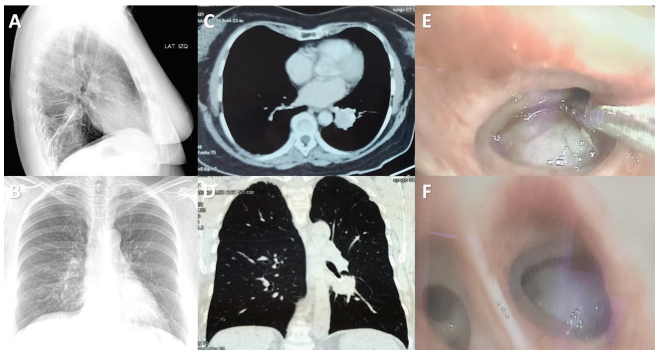

Figure 1. Preoperative imaging studies. Posteroanterior and lateral view chest radiograph showing a calcified nodular lesion in the left hilar region associated with reticular lesions and bronchiectasis **(A,B)**, calcified nodular lesion involving the endobronchial region of the left lower lobe **(C,D)**, a flexible bronchoscopic study identifying a friable, pearly white, endobronchial lesion in the left lower lobe **(E,F)**.

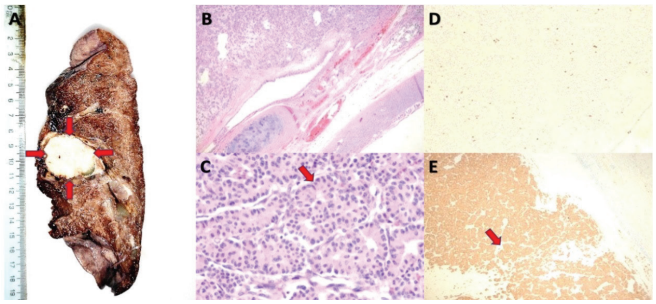

Figure 2. Anatomo-pathological studies. Operative specimen corresponding to the endobronchial region of the left lower lobe showing a solid whitish tumor lesion occupying 98% of the lumen (3x2.5 cm) (Arrow) **(A)**. Haematoxylin-Eosin staining shows fragments of mucosa and bronchial wall with chronic inflammation and fibrosis; at the level of the bronchial wall, small cellular nests with organoid patterns with characteristics suggestive of a neuroendocrine lesion can be seen (Arrow) **(B,C)**. Chromogranin staining showed positivity of the tumor nests and a Ki-67 (proliferation index/immunohistochemistry) of 4%, compatible with a neuroendocrine or pulmonary carcinoid tumor (Arrow) **(D,E)**.

Discussion

Carcinoid tumors can produce vasoactive hormones, whose activity rarely conditions the appearance of carcinoid syndrome (8%) and its crises (3%) as reported by Savu et al, who described this presentation in 3 out of 98 patients, characterized by tachycardia, arterial hypertension, flushing, bronchospasm and accelerated digestive transit [5]. Differential diagnoses include asthma, airway obstruction by aspirated foreign body, metastases, bronchopulmonary carcinoma, benign pulmonary nodule, or endocrinological entities such as Cushing's syndrome, which can occur in up to 2 % of AC and TC due to ectopic production of adrenocorticotropic hormone (ACTH) or acromegaly, due to ectopic production of growth hormone-releasing hormone (GHRH) or insulin-like growth factor 1 (IGF-1). ACTH, growth hormone (GH) testing is not routinely performed unless there are related symptoms.

They are usually visualized as solitary pulmonary nodules predominantly in segmental or subsegmental bronchi (80%), in some cases with calcifications, and in up to 75% they are associated with endobronchial lesions as in the present case [4]. Histopathology of TC and AC consist of a uniform organoid growth pattern with cytological features consisting of a moderate amount of eosinophilic cytoplasm with an eosinophilic matrix, with a variety of histological patterns in both, including spindle cell, trabecular, palisade, glandular, follicular, rosette, pink, clear cell, and papillary patterns. Identification and classification can be difficult with immunohistochemistry being important, which points towards a neuroendocrine nature by being positive for synaptophysin, chromogranin, and CD56. However, these can be positive in 30% of cases of lung adenocarcinoma and squamous cell carcinoma, as well as metastatic carcinomas of the breast, prostate, and other sites, and should therefore be considered as differential diagnoses. TTF-1 expression in TC and AC is varied. Most carcinoids stain for cytokeratins, but up to 20% to 25% may be keratin negative. Ki-67 staining shows a low proliferation rate in TC, usually less than 5% while in AC it is higher, usually between 5% and 20%. The proliferation rate may be more useful in small biopsies to separate TC and AC from SCLC, respectively. Ki67 is of limited value in tumors of lung origin, however, it has been estimated that a value > 5% in AC and > 10%, in general, are associated with poor prognosis [6]. The transcription factors TTF-1, CDX-2, and PDX-1 allow differentiation of primary lung origin, being site-specific for lung, gastrointestinal and pancreatic origins, respectively.

Approximately 80 % of low-grade (typical) and 60 % of intermediate-grade (atypical) pulmonary carcinoids express somatostatin receptors by immunohistochemistry and can be imaged using positron emission tomography (PET) or somatostatin receptor scans (OctreoScan) [7]. Typically, 90% are confined to the bronchi and 10% to regional lymph nodes; however, in our case, the nodal staging was negative. As with any neoplastic process, prognosis depends on histological type, stage, and metastatic involvement. Surgical management is of choice and even curative in some cases, there is no standardization, with complete anatomical resection plus mediastinal lymphadenectomy being the most commonly described, however, options range from wedge resection, lobectomy, pneumonectomy or sleeve resection together with mediastinal lymph node study. The latter is controversial, due to the low potential for nodal metastasis of non-active AC and TC described. However, in endocrinologically active tumors a high nodal metastatic potential is presumed, as demonstrated by Seastedt et al who after evaluating 68 cases of pulmonary carcinoids associated with Cushing's syndrome found mediastinal nodal involvement in 37%, with an overall incidence of persistence/recurrence of 16.2% and with a median time to recurrence of 55 months (Range, 18-152 months). He also reported a disease-free time of 12.7 years [8].

Girelli et al analyzed 325 patients with pulmonary carcinoids undergoing complete resection (236 with lymph node involvement and 89 without lymph node involvement), of these 23.6% had TC, 39.3% AC, and 37.1 % large cell neuroendocrine carcinoma. 58.4 % underwent lobectomy, and 21.3 % pneumonectomy, with a mean tumor size of 11-130 mm. Mortality analyzed after 4.0 years of follow-up reached 5.1 %. For TC and AC, the 5-year survival was 89 % and 78 % at 10 years, with a worse prognosis for large cell neuroendocrine carcinoma, 47 % at 5 years, and 41 % at 10 years [9]. Follow-up is carried out taking into account the high potential for recurrence, by clinical and radiological examination. At 3 and 6 months and depending on whether it is TC or AC, annually and semi-annually respectively. Bronchoscopic control may even be indicated in the case of endoscopic resections. These measures should be maintained even for life, with a 10-year survival rate of approximately 90%. The patient underwent follow-ups at 3, 6, and 9 months with no evidence of recurrence [10]. Somatostatin receptor (SRS)-based therapies such as 177-Lu-DOTATATE is an effective and safe option in patients with somatostatin receptor (SRS)-positive (TC)- and (AC)-positive progression. Zidan et al reported in 48 patients after 42 months of follow-up a 33% mortality, a progression-free survival of 23 months, and an overall survival of 59 months [7]. In cases where surgical management is not possible, other therapies such as local radiotherapy should be considered and combined with surgery in cases of AC and Large Cell Neuroendocrine Carcinoma.

In conclusion, it should be remembered that the prognosis and survival of these patients also depend on the histological type of clinical stage, with surgery being the treatment of choice even in locally advanced stages.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support.

Ethical approval

The present article is approved for the committee ethical (iO56-94/22) of Department Thoracic Surgery.

Authors' contributions

All authors contributed equally to the idea, data collection, drafting and final approval of the manuscript.

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Current Thoracic Surgery

To cite this article: Karaçam V, Sağıroğlu G, Karcı E, Mutlu F, Kaya İ. First awake uniportal video assisted thoracoscopic lobectomy in Turkey. Curr Thorac Surg 2023; 8(3): 155-159.

Case Report

First awake uniportal video assisted thoracoscopic lobectomy in Turkey

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ABSTRACT

As in all surgical branches, the importance of minimally invasive surgery in thoracic surgery has been increasing in recent years. Especially in the last decade, the preference of thoracic surgeons is mostly in favor of VATS. As a result of today's developing technology and experience, minimally invasive surgery is not limited to surgical technique only, and less invasive non-intubated methods have been started to be used in anesthesia applications. While non-intubated (awake) VATS is usually applied for reasons such as pleural effusion, empyema, hemothorax, pneumothorax, it is now preferred for anatomical resection of the lung. We also prefer the awake VATS method in suitable patients in our clinic. In this study, we aimed to talk about our case in which we performed left lower lobectomy and mediastinal lymph node dissection with awake uVATS (uniportal VATS) method in our clinic.

Keywords: awake anesthesia, uniportal VATS, lobectomy

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Doi: 10.26663/cts.2023.0028
Received 28.03.2023 accepted 24.04.2023

Introduction

Video-assisted thoracic surgery (VATS) is currently the gold standard minimally invasive method. In parallel with the increasing experience, surgeons tend towards the uniportal approach instead of multiportal approach. Uniportal VATS (uVATS) is the most advanced of the minimally invasive methods and has been shown to provide advantages such as less postoperative pain and shorter hospital stay in the patient [1].

Non-intubation anesthesia techniques have been used in non-thoracic surgeries for a long time. However, in recent years, non-intubation surgery has been used especially in thoracoscopic diagnosis and treatment applications. With the development of the equipment used in VATS, it has allowed the surgery to be performed without general anesthesia and without the need for double-lumen intubation. Thanks to the combination of VATS and non-intubation method, patients who cannot handle general anesthesia can be operated on. As a result of lung collapse caused by air entering the thorax, operations can be performed with open pneumothorax without the need for a double-lumen tube [2].

With the publication of new data in many centers around the world in recent years, it is thought that uniportal awake VATS (auVATS) will continue to be performed reliably in an increasing number of patients. We aimed to discuss this case in the light of the literature, since it is the first case in our country who underwent auVATS lobectomy under epidural anesthesia.

Case Report

A 67-year-old male patient with the diagnosis of diabetes mellitus and ulcerative colitis was referred to our clinic after a nodular lesion in the left lower lobe was detected in the abdominal computed tomography (CT) performed due to abdominal pain. Thorax CT revealed a 15x11 mm nodular lesion with spiculated contours in the posterobasal segment of the left lung lower lobe. The patient had a 20 pack/year smoking history and had no smoking history for 15 years. No pathological finding was detected in the physical examination of the patient who described dyspnea with exertion. On positron emission tomography (PET), increased pathological uptake (SUVmax: 3.4) in the nodular lesion in the posterobasal segment of the left lung lower lobe, and increased pathological uptake in the left lower paratracheal, subcarinal, and left hilar lymph nodes (SUVmax: 2.2) were detected (Figure 1). There was also diffuse uptake in the colon.

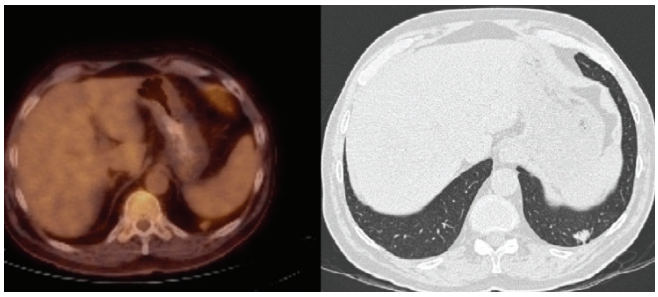

Figure1. Preoperative thorax tomography and Pet/bt images showing the nodule.

Colonoscopy was performed due to pathological uptake in the colon and endobronchial ultrasonography (EBUS) was performed due to uptake in the mediastinum. The biopsy result taken at colonoscopy resulted in active chronic colitis. No malignancy was observed as a result of needle aspiration biopsy taken from mediastinal lymph node stations 4R, 7 and 11L with EBUS. No space-occupying lesion was detected in brain MRI (magnetic resonance imaging).

In the pulmonary function test (PFT), FEV1 (forced expiratory volume in the first second) was 2.20 liter (78%), FVC (forced vital capacity) was 2.89 L (76%). Stereotactic Body Radiation Therapy was recommended for local treatment for the patient who refused the operation due to general anesthesia and intubation phobia. As the patient also refused radiotherapy, the patient was informed about awake surgery. AuVATS was planned for the case after obtaining informed written consent. Also, written informed consent was obtained from the patient for the publication of his data.

Anesthesia Technique

In the operating room, intravenous peripheral catheter was placed in the forearm and a continuous infusion of isotonic 0.9% NaCl solution was started. The patient was monitored with five lead electrocardiography, invasive arterial blood pressure, heart rate, pulse oxygen saturation (SpO2), end tidal cardondioxide (ETCO2), respiratory rate, axillary body temperature, and urine output. Mean arterial blood pressure (MAP), heart rate and SpO2 were measured in the perioperative period. Patient was arterial blood pressure value as normal but the SpO2 value is 90% or less was regarded as hypoxic.

Lidocaine (Jetmonal 2%, Adeka Pharmaceutical, Turkey) was administered by inhalation 30 minutes before operation due to suppress cough reaction in the intraoperative period [3].

In the sitting position thoracic epidural anesthesia was performed by insertion of an epidural catheter at the T5-6 interspace with an 18-gauge Tuohy needle (B-Braun Medical, Abbott, Turkey) via the saline loss of resistance technique. The catheter was advanced 3 cm cephalically and a test dose of 20 mg of 2% lidocaine was given to rule out subarachnoid or intravascular placement of the catheter. After preparation of a 0.125% solution of bupivacaine (Buvasin 0.5%, Vem Pharmaceutical, Turkey) with 1 μg/ml fentanyl (Talinat 0.1 mg/2 mL, Vem Pharmaceutical, Turkey) a bolus dose of 10 ml was given followed by a continuous infusion of 0.1 mL/kg/h through catheter intraoperatively. This solution was continued postoperatively for 24 hours. Pain intensity was evaluated by using a 10 cm visual analog scale (VAS), where zero represented no pain and 10 cm represented worst possible pain. During the surgery and postoperatively, we increased the continuous infusion dosage by 10% in patient whose VAS score was 4 or greater and reduced it in patient who had respiratory depression (rate, 8 breaths/min) by 10%.

Sensory blockade was assessed by pin prick every 5 min for up to 25 min after epidural injection. Loss of sensation from the T2 and T8 dermatomes was achieved. The surgery was started only when this was no response by the patient to a pinprick in the surgical field. Target-controlled infusion of remifentanil was used.

During the thoracoscopic procedure, via a face mask, at least 2-4 L/min oxygen was continuously administered along with detection of ETCO2. Patient received 4-6 L/min oxygen and sedated by 2 mg/kg/h propofol (Propofol 1%, Fresenius Pharmaceutical, Turkey). Sedation level was kept at cooperated, oriented and tranquilized at Wilson 2 level and the sedation was terminated during wound closure [4]. We terminated infusion of remifentanil for about 5 minutes before the end of surgery.

After insertion of catheters, hypotension (MAP being 20% of the baseline value or lower) was administered with a bolus of isotonic fluid and an intravenous 10 mg of ephedrine bolus (Ephedrine, Osel Pharmaceutical, Turkey). Bradycardia (decrease in heart rate below 45 beats/min) was treated with intravenous atropine (Atropin sulfate, Biofarma Pharmaceutical, Turkey) at a dose of 0.01 mg/kg. Respiratory depression (respiratory rate below 8 per min) was treated with 100% oxygen supplementation through a face mask.

Surgical Technique and Postoperative Follow-up

For thoracoscopy, a 3 cm incision was made in the fifth intercostal space and the left hemithorax was accessed with the help of a thoracoport. After performing an open pneumothorax, the ipsilateral lung gradually collapsed. In order to prevent coughing during thoracoscopic manipulation, the tracing of the vagus nerve was followed and intrathoracic vagal block was created at the level of the aorticopulmonary window and hilum by injecting 2 mL of 0.25% bupivacaine (Buvacin 0.5%, Vem İlaç Sanayi, Turkey). Wedge resection was performed on left lower lobe and underwent intraoperative frozen section analysis. After fifty five minutes, the frozen result was reported as "primary malignancy of the lung, compatible with adenocarcinoma", the patient underwent left lower lobectomy. Left lower lobectomy and mediastinal lymph node dissection 6, 7, 10, 11 were performed through the same incision. A 24 F (french) thoracic drain was placed and the layers were closed in accordance with the anatomical plan. In order to reexpand the collapsed lung of the patient, the patient was asked to take a deep breath and cough. The operation time was 210 minutes in total. The patient, who was kept under observation in the recovery unit for half an hour after the operation, was taken to the ward and mobilized in the 2nd postoperative hour.

For postoperative VATS incision pain, an infusion of fentanyl and bupivacaine was continued through the epidural catheter for 24 hours. In addition, paracetamol (Paracerol, Polifarma İlaç Sanayi, Turkey) and diclofenac (Dilcomec 75 mg, Abdi İbrahim İlaç Sanayi, Turkey) were used for drain pain and pain control after removal of the epidural catheter. The patient did not have any complication. The drain of the patient was terminated on the second postoperative day. The patient was discharged healthy on the third day.

Discussion

Today, VATS is the least invasive way of operating lung pathologies. Compared to multiportal VATS, uVATS provides less postoperative pain, less residual paresthesia, and shorter hospital stay [5]. The uniportal approach without general anesthesia has become the least invasive method. Operations performed without intubation minimizes the complaints of ventilation-related lung injury [6], intubation-related airway injury [7], and anesthesia-related nausea and vomiting. In this way, since general anesthesia is not applied, it accelerates the return to daily life.

Some criteria should be considered in the selection of patients who will undergo awake VATS. Although it is a method that can be preferred in cases with reduced lung function who are at high risk for general anesthesia due to advanced age and comorbidities this technique should not be used in the presence of obesity, previous surgeries, adhesions, persistent cough, and inexperienced anesthesiologists and surgeons [8].

While awake VATS was used for spontaneous pneumothorax, pleural biopsy, pleural effusion [9,10], El-Abdullatief et al performed lung resections for awake patients for the first time in 2007. In this series of 79 cases, with awake epidural catheter and supression of the cough reflex with stellate ganglion blockade, they achieved more positive results in terms of returning to daily life and complications compared to resections performed under general anesthesia. However, they did not clearly state whether major resection cases were performed with VATS [11]. In our clinic, it is frequently used in operations such as pleural biopsy, empyema and pleural effusion drainage, hemothorax-pneumothorax surgery in patients who are not suitable for general anesthesia or intubation (in patients with advanced chronic obstructive pulmonary disease, advanced age, and cardiopulmonary failure).

In 2011, Chen et al presented their first experience with awake VATS lobectomies. In this study, with the three-port VATS technique; concluded that awake VATS lobectomy can be reliably performed in early stage non-small cell lung cancer using an epidural catheter and vagal blockade. They emphasized that intrathoracic vagal nerve blockade should be performed because unexpected lung movement may occur due to cough reflex and spontaneous breathing during hilar dissection [12]. One year later, the same team demonstrated the safety and feasibility of awake lung resections in another case series of 285 patients who underwent VATS resection under awake epidural anesthesia [13]. In our case, anesthetic and analgesic infusion was applied with an epidural catheter, and it was successfully performed by applying vagal nerve blockade to prevent cough reflex.

In 2014, Guo et al [14] achieved good results in segmentectomies performed while awake without intubating. In 2015, Hung et al [15] reported a study in which they successfully performed VATS lobectomy or segmentectomy with a 3-port approach under thoracic epidural anesthesia in a series of 238 cases.

When we look at the literature, while awake VATS lobectomies are usually performed from two or more ports, the first awake uniportal VATS lobectomy was reported in 2014 by Rivas et al. The case who underwent right middle lobectomy; it was successfully applied without the use of epidural catheter and intubation tube, without the need for intrathoracic vagus blockade, only by injecting 5 ml of levobupivacaine (5 mg/mL) into the skin and intercostal space for intercostal nerve blockade. Sevoflurane and remifentanil infusion were administered for sedation during the surgery. They stated that the single-port approach and awake VATS can be applied safely and more comfortably for the patient [16]. In a recent series in 2020, Furak et al compared awake and intubated uVATS lobectomy cases; found that awake VATS provides fewer postoperative complications, shorter hospital stay and follow-up with a drain [17]. In our clinic, the uniportal approach is mostly used in patients undergoing resection with VATS, and uVATS lobectomy was successfully performed in this case. Our case was mobilized in the second postoperative hour, the drain was terminated on the second postoperative day and patient was discharged on the third postoperative day. No complications were observed in the postoperative period.

The first published case of VATS lobectomy under awake epidural anesthesia in Turkey was presented in 2021 by Özen et al [18]. Right upper lobectomy with two ports was successfully performed by placing an epidural catheter under the guidance of ultrasonography. However, when we look at the literature, our study is the first case of awake uniportal VATS lobectomy with epidural anesthesia in Turkey.

Bleeding requiring thoracotomy that may occur during the operation is the biggest problem of awake surgery. Therefore, it should be performed by surgeons experienced in VATS. Giving the patient a suitable position during the operation is important in making the operation more comfortable. However, depending on the duration of the operation, shoulder pain may be seen due to the position. Since epidural anesthesia is not effective, the patient may need extra analgesia. In our case, only shoulder pain was observed in the first 24 hours postoperatively, and therefore 100 mL of paracetamol (10 mg/mL) was given iv.

In conclusion, lung resections with uVATS under awake epidural anesthesia can be performed successful-

ly and without complications with an experienced surgical and anesthesia team. Although its long-term results are unknown, it represents an important alternative for high-risk patients for intubation and general anesthesia. As the developments in anesthesia and thoracic surgery around the world continue, the number of these cases will gradually increase in the future and will gain an important and reliable place in thoracic surgery.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support.

Authors' contributions

VK,GS,EK,FM,İK: conceived and designed the current case report, co-wrote the paper, collected the clinical data. The authors discussed the case under the literature data together and constituted the final manuscript.

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To cite this article: Gungor BO, Karapolat S, Topaloğlu O, Turkyilmaz A. Tuberous sclerosis and chylothorax. Curr Thorac Surg 2023; 8(3): 160-162.

Case Report

Tuberous sclerosis and chylothorax

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ABSTRACT

A 48-year-old female with tuberous sclerosis admitted with shortness of breath. The chest radiography revealed a left sided hydropneumothorax. A tube thoracostomy was and 2000 cc of chylous fluid was drained. As the daily drainage was not reduced, ligation of the thoracic duct was performed. The patient was discharged uneventfully. In cases of tuberous sclerosis presenting with chylothorax, a successful treatment can be applied with early thoracic duct mass ligation.

Keywords: tuberous sclerosis, chylothorax, surgery

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Doi: 10.26663/cts.2023.0029
Received 30.05.2023 accepted 17.08.2023

Introduction

Tuberous sclerosis is a rare autosomal dominant inherited disorder characterized by classic triad of epilepsy, mental retardation, and angiofibroma. It affects kidneys, heart, liver, bones, lungs, as well as central nervous system and skin. Lung involvement is usually similar to that seen in lymphangiomatosis, and characterized by alveolar smooth-muscle proliferation, and cystic destruction of lung parenchyma. All of these cases reported are female, and are often manifested by spontaneous pneumothorax, lymphadenopathy, angiomyolipomas and chylothorax. Chylothorax occurs when lymphatic fluid accumulates in the pleural cavity due to the impairment or obstruction of the thoracic duct and is a life-threatening condition. Chylothorax develops during tuberous sclerosis can be refractory and difficult to treat [1].

Here, we present the treatment process of chylothorax in a female patient diagnosed with tuberous sclerosis along with literature data.

Case Report

A 48-year-old woman was admitted to our clinic with shortness of breath and chest pain. The patient history included 8 years of follow-up and treatment with the diagnosis of tuberous sclerosis. Physical examination showed decreased breathing sounds in the left hemithorax. The patient underwent left tube thoracostomy due to the left hydropneumothorax on the posteroanterior chest X-ray, and 2000 cc chylous fluid was drained (Figure 1A). Thoracic tomography showed diffuse, well circumscribed, thin-wall cystic lesions in both lung parenchyma and left pleural effusion (Figure 1B). Biochemical testing of the fluid showed that triglyceride value was 435 mg/dL. Oral intake of the case discontinued and total parenteral nutrition was initiated. Daily drainage ranged from 800-1000 cc. Ultrasound and fluoroscopy-guided lymphangiography carried out on day 4 did not show lymphatic leakage in the thoracic duct (Figure 2). Since the daily drainage was not reduced, right posterior thoracotomy was performed under general anesthesia on day 7. In exploration, multiple bullous regions on the visceral pleura were seen and then ligation of the thoracic duct was performed (Figure 3A and 3B). The patient who did not develop complications was discharged on 3rd postoperative day. Postoperative follow up of 6 months was clinically and radiologically uneventful. Written informed consent was obtained from the patient for the publication of her data.

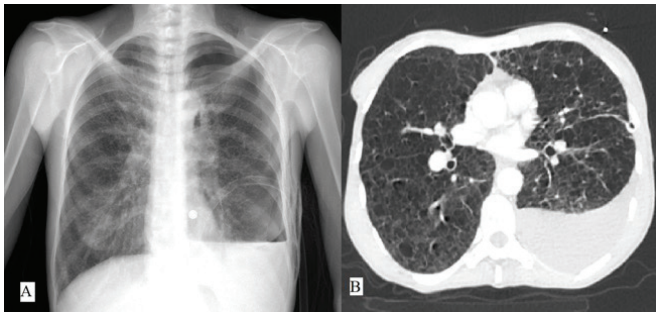

Figure 1. Posteroanterior chest X-ray showing left hydropneumothorax and chest tube **(A)**, thoracic tomography revealed diffuse, thin-wall cystic lesions in both lung parenchyma and left pleural effusion **(B)**.

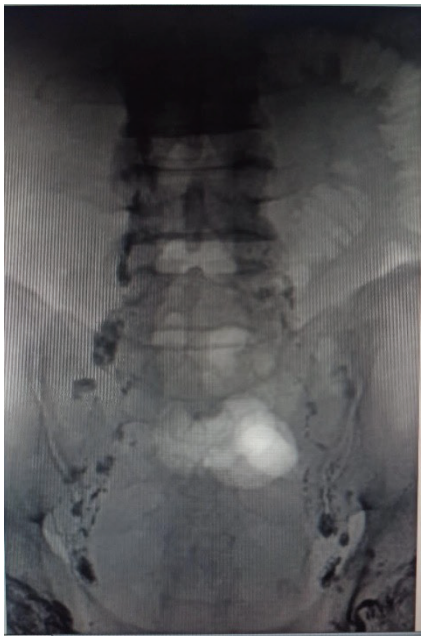

Figure 2. Lymphangiography showed an intact thoracic duct.

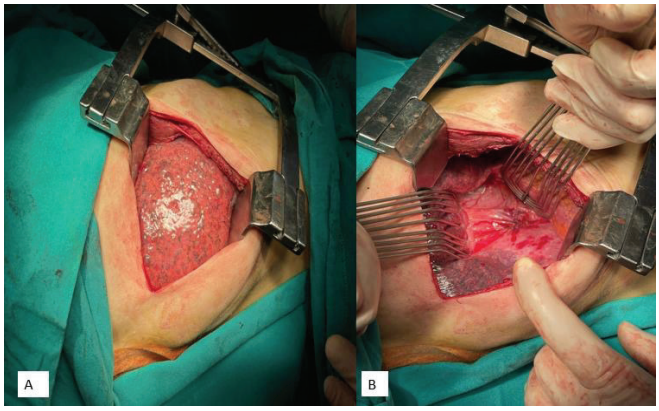

Figure 3. Operative view showing bullous areas of the lung **(A)**, appearance following mass ligation of the thoracic duct **(B)**.

Discussion

Although chylothorax is a benign condition, it can cause severe morbidity and mortality due to malnutri-

tion, dehydration, metabolic acidosis, cachexia and immunodeficiency [2]. In recent years, somatostatin and its analog, octreotide, have been used in the treatment of chylothorax [3]. It is crucial to determine the etiology immediately and to plan conservative and/or surgical intervention. As in this case, in patients with severe comorbid diseases including tuberous sclerosis, if there is no response to conservative treatment in the early period, it should not be persisted and invasive interventions should be considered. In fact, since the patient had a diagnosis of tuberous sclerosis, fluoroscopic percutaneous thoracic duct embolization was first considered. Under normal circumstances, the success rate of this minimally invasive procedure varies between 45-100% with low morbidity, and it can be safely performed at an earlier period compared to surgery even in debilitated person [2]. Thoracic duct embolization is particularly used in traumatic chylothorax with success rates above 90% as first-line therapy. However, the success rate in non-traumatic chylothorax is lower, especially in cases with no thoracic duct occlusion or extravasation on lymphangiography [4]. In our case, embolization was not performed by invasive radiology team since lymphangiography did not show thoracic duct leak.

Thoracic duct ligation remains the gold standard in the surgical treatment of chylothorax. This procedure involves application of mass ligation of the tissue between the aorta and the azygos vein above the aortic hiatus allowing optimal exposure by thoracoscopic approach or by posterior mini-thoracotomy through the 7th or 8th intercostal space on the right. Non-absorbable sutures are usually used in this technique [5]. However, we preferred absorbable polyglactin sutures because they reported to cause less tissue reaction. To reduce the risk of recurrence, the surrounding parietal pleura was bilaterally sutured into the corresponding sides to produce a regional adhesion following mass ligation.

In conclusion, chylothorax may occur during the course of tuberous sclerosis. Surgical thoracic duct ligation in the early period will prevent worsening of the general condition of the patients.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support.

Author Contributions

B.O.G., S.K. and O.T. have given substantial contributions to the literature search, data collection, study design, analysis of data, manuscript preparation and review of manuscript, author B.O.G., S.K., O.T. and A.T., analysis interpretation of the data and review of manuscript. All authors have participated to drafting the manuscript, author B.O.G., S.K. and O.T. revised it critically. All authors read and approved the final version of the manuscript. All authors contributed equally to the manuscript, read and approved the final version of the manuscript.

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Publication Ethics and Malpractice Statement

The Current Thoracic Surgery is electronic peer reviewed international journal committed to upholding the possible highest standards of publication ethics. In order to provide our readers with a journal of highest quality we state the following principles of Publication Ethics and Malpractice Statement. All articles not in accordance with these standards, will be removed from the publication if malpractice is discovered at any time even after the publication. The Current Thoracic Surgery is checking all papers in a double-blind peer review process. We also check for plagiats and research fabrication (making up research data); falsification (manipulation of existing research data, tables, or images) and improper use of humans or animals in research. In accordance with the code of conduct we will report any cases of suspected plagiarism or duplicate publishing. The Current Thoracic Surgery reserves the right to use plagiarism detecting software to screen submitted papers at all times.

Authors must ensure that they have written original works. In addition they must ensure that the manuscript has not been issued elsewhere. Any work or words of other authors, contributors, or sources should be appropriately credited and referenced. Authors are also responsible for language editing before submitting the article. Authors submitting their works to the journal for publication as original articles confirm that the submitted works represent their authors' contributions and have not been copied or plagiarized in whole or in part from other works without clearly citing. Any work or words of other authors, contributors, or sources (including online sites) should be appropriately credited and referenced. All authors should disclose financial or other conflict of interest that might influence the results or interpretation of their manuscript (financial support for the project should be disclosed). When an author discovers a significant error or inaccuracy in his/her own published work, it is the author's obligation to promptly notify the journal editor and cooperate with the editor to retract or correct the paper. An author agrees to the license agreement before submitting the article. All articles must be submitted using online submission procedure. Submitting a paper simultaneously to more than one publication at a time is a breach of publications ethics. Before publication of an accepted manuscript, each author will be required to certify that he or she has participated sufficiently in the work to take responsibility for a meaningful share of the content of the manuscript, and that this participation included:

1. Conception or design of the experiment(s), or collection and analysis or interpretation of data;

2. Drafting the manuscript or revising its intellectual content; and

3. Approval of the final version of the manuscript to be published.

Editors must ensure a fair double-blind peer-review of the submitted articles for publication. They will strive to prevent any potential conflict of interests between the author and editorial and review personnel. Editors will also ensure that all the information related to submitted manuscripts is kept as confidential before publishing. Editor-in-Chief will coordinate the work of the editors.

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Public trust in the peer review process and the credibility of published articles depend in part on how well conflict of interest is handled during writing, peer review, and editorial decision making. Conflict of interest exists when an author (or the author's institution), reviewer, or editor has financial or personal relationships that inappropriately influence (bias) his or her actions (such relationships are also known as dual commitments, competing interests, or competing loyalties). These relationships vary from those with negligible potential to those with great potential to influence judgment, and not all relationships represent true conflict of interest. The potential for conflict of interest can exist whether or not an individual believes that the relationship affects his or her scientific judgment. Financial relationships (such as employment, consultancies, stock ownership, honoraria, paid expert testimony) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, and of science itself. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion.

So authors should declare that there is no conflict of interest and also, if there is any, the status for their financial support should be clear in the cover letter and within article.

Decleration of sponsorship

The authors should describe the role of the study's sponsors in the following areas: a. designing the study, b. collecting, analyzing, and interpreting the data, c. writing the report.

Corrections, Retractions and Expression of Concern

It is presumed that manuscripts report on work based on honest observations. However occasionally information becomes available with may contradict this. In such situations CTS apply Committee on Publication Ethics guidelines on corrections, retractions and expressions of concern.

Corrections

Errors in published papers may be identified requiring publication of a correction in the form of a corrigendum or erratum. Because articles can be read and cited as soon as they are published, any changes thereafter could potentially impact those who read and cited the earlier version. CTS provides authors with an opportunity to review article proofs prior to publication with the express goal of ensuring accuracy of the content. Publishing an erratum or corrigendum increases the likelihood readers will find out about the change and also explains the specifics of the change.

Corrigenda and Errata will be published on a numbered page and will contain the original article's citation. Cases where these corrections are insufficient to address an error will be dealt with on a case-by-case basis by the Editor in Chief. Inadequacies arising from the normal course of new scientific research are not within the scope of this and will require no correction or withdrawal.

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Infringements of professional ethical codes, such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like. Occasionally a retraction will be used to correct errors in submission or publication. The retraction of an article by its authors or the editor under the advice of members of the scholarly community has long been an occasional feature of the learned world. Standards for dealing with retractions have been developed by a number of library and scholarly bodies, and this best practice is adopted for article retraction by CTS:

A retraction note titled "Retraction: [article title]" signed by the authors and/or the editor will be published in the paginated part of a subsequent issue of the journal and listed in the contents list. In the electronic version, a link will be made to the original article. The online article will preceded by a screen containing the retraction note. It is to this screen that the link resolves; the reader can then proceed to the article itself. The original article will be retained unchanged save for a watermark on the .pdf indicating on each page that it is "retracted."

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Where substantial doubt arises as to the honesty or integrity of a submitted or published article it is the Editor in Chief's responsibility to ensure that the matter is adequately addressed, usually by the authors' sponsoring institution. It is not normally the Editor in Chief's responsibility to carry out the investigation or make a determination. The Editor in Chief should be promptly informed of the decision of the sponsoring institution and a retraction printed should it be determined that a fraudulent paper was published. Alternatively, the Editor in Chief may choose to publish an expression of concern over aspects of the conduct or integrity of the work.

Withdrawal

Articles may be withdrawn by corresponding author before accepting for publication. If it is accepted, it could be used only for Articles in Press which represent early versions of articles and sometimes contain errors, or may have been accidentally submitted twice. Occasionally, but less frequently, the articles may represent infringements of professional ethical codes, such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like. Articles in Press (articles that have been accepted for publication but which have not been formally published and will not yet have the complete volume/issue/page information) that include errors, or are discovered to be accidental duplicates of other published article(s), or are determined to violate our journal publishing ethics guidelines in the view of the editors (such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like), may be "Withdrawn" from CTS. Articles which have been published under an issue could not be withdrawn.

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When allegations concern authors, the peer review and publication process for the manuscript in question will be halted while the process above is carried out. The investigation described above will be completed even if the authors withdraw their paper, and the responses below will still be considered. In the case of allegations against reviewers or editors, they will be replaced in the review process while the matter is investigated. For further information visit "Useful links".

Data Sharing Policy

Current Thoracic Surgery requires authors to submit a data-sharing statement form and register a data-sharing plan when registering a clinical trial. The ICMJE's data sharing statement policy asks authors to submit a data-sharing statement for randomized clinical trials. The ICMJE's policy regarding trial registration is explained at (http://www.icmje.org/icmje-recommendations.pdf).

Accordingly, the data sharing statements must indicate the following:

whether individual deidentified participant data (including data dictionaries) will be shared,

what data in particular will be shared,

whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.),

when the data will become available and for how long,

by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism).

Authors must provide a data-sharing statement at submission to indicate whether data will be shared according to the statements written above.

Please visit http://www.icmje.org/icmje-recommendations.pdf that provides illustrative examples of data sharing statements that would meet these requirements.

Authors of secondary analyses using shared data must attest that their use was in accordance with the terms (if any) agreed to upon their receipt. They must also reference the source of the data using its unique, persistent identifier to provide appropriate credit to those who generated it and allow searching for the studies it has supported. Authors of secondary analyses must explain completely how theirs differ from previous analyses. In addition, those who generate and then share clinical trial data sets deserve substantial credit for their efforts. Those using data collected by others should seek collaboration with those who collected the data. As collaboration will not always be possible, practical, or desired, the efforts of those who generated the data must be recognized.

Statistical Knowledge

The statistical method used should be reported in a way that a reader whoever could reach the original data could understand the results. The terms used, abbreviations, symbols, the pc programme used and the statistical method should all be defined.

When reporting the results, especially when giving means and percentages, two digits should be given after the comma (112.20 or 112.21 instead of 112.2). P, t, Z values are exceptional and three digits should be given after the comma ($p = 0{,}001$, instead of $p < 0{,}05$).

Briefly, except whole numbers, two digits after the comma should be given, but for statistical values like p,t,z,F,Chi-square, three digits after the comma should be given. When presenting p values, the exact p value together with the test statistics should be given, except for the case when this value is smaller than one percent or one per thousand (this time $p < 0.01$ or $p < 0.001$, respectively should be given).

Preparation of Manuscript

Cover Letter

The Current Thoracic Surgery requires authors to disclose in the "cover letter" any commercial association (eg, employment, direct payments, stock holdings, retainers, consultantship, patent licensing arrangements, or honoraria) that might pose a conflict of interest issue concerning the manuscript. All funding sources supporting the work should be acknowledged in a footnote. Also authors should mention that none of the material in the manuscript has been published previously, and that none of this material is currently under consideration for publication elsewhere. This includes symposia, transactions, books, articles published by invitation, and preliminary publications of any kind except an abstract of 400 words or fewer.

Style and Format

Manuscripts should be double-spaced with 3-cm margins on all sides of the page, in Times New Roman font. Every page of the manuscript, including the title page, references, tables, etc., should be numbered. All copies of the manuscript should also have line numbers starting with 1 on each consecutive page.

Symbols, Units and Abbreviations

In general, the journal follows the conventions of Scientific Style and Format, The CSE Manual for Authors, Editors, and Publishers, Council of Science Editors, Reston, VA, USA (7th ed.). If symbols such as ×, μ, η, or ν are used, they should be added using the Symbols menu of Word. Degree symbols (°) must be used from the Symbol menu, not superscripted letter o or number 0. Multiplication symbols must be used (×), not the letter x. Spaces must be inserted between numbers and units (e.g., 3 kg) and between numbers and mathematical symbols (+, –, ×, =, <, >), but not between numbers and percent symbols (e.g., 45%). Please use SI units. All abbreviations and acronyms should be defined at first mention. Latin terms such as et al., in vitro, or in situ should not be italicized.

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Research articles should be divided into the following sections. Principal sections should be Introduction, Materials and Methods, Results, Discussion, Acknowledgements and References sections. Please see below for information about other types of manuscripts.

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The first page should contain the full title in sentence case, the full names (last names fully capitalized) and affiliations (in English) of all authors (University, Faculty, Department, City, Country), and the contact address and e-mail for the clearly identified corresponding author.

Abstract

An informative abstract of not more than 250 words must accompany each manuscript. The abstract must be structured to include the study's background, materials and methods, results, and conclusions and key words under 5 separate headings. Abstracts of review articles should be a brief overview of the main points from the review.

Keywords

Please provide at least 3 key words or phrases to enable retrieval and indexing. Acronyms should be avoided.

Always try to use terms from the Medical Subjects Headings (MeSH) list from PubMed https://www.ncbi.nlm.nih.gov/pubmed.

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This should argue the case for your study, outlining only essential background, and should not include the findings or the conclusions. It should not be a review of the subject area, but should finish with a clear statement of the question being addressed.

Materials and Methods

Explain clearly but concisely your clinical, technical, or experimental procedures. Previously published papers related to the methods should be cited with appropriate references. Brand names and company locations should be supplied for all mentioned equipment, instruments, chemicals, etc.

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Findings must be described without comment. The same data or information given in a Table must not be repeated in a Figure and vice versa. It is not acceptable to repeat extensively the numbers from Tables in the text or to give lengthy explanations of Tables or Figures.

Discussion

Statements from the Introduction and Results sections should not be repeated here. The final paragraph should highlight the main conclusions of the study. Names of funding organizations should be written in full.

References

In the text, references should be identified using numbers in square brackets in which they appear consecutively. The titles of journals should be abbreviated according to the style used in Index Medicus. Ageneral guide limit the number of references to 25 for original articles, to 6 for case reports and to 85 for reviews. For articles with 1 to 6 authors, list all authors. For articles more than 6 authors, list the first 6 authors followed by "et al.". Do not use individual sets of parentheses for citation numbers that appear together, e.g., [2,3,5-9], not [2],[3],[5]–[9]. For other styles of publication or Internet articles, see http:// www. nlm.nih.gov/ bsd/ uniform_requirements.html References should be formatted as follows (please note the punctuation and capitalization)

Journal titles should be abbreviated according to ISI Web of Science abbreviations. Authors are solely responsible for the accuracy and completeness of references.

Articles in Journals

Özpolat B, Gürpınar ÖA, Ayva EŞ, Gazyağcı S, Niyaz M. The effect of Basic Fibroblast Growth Factor and adipose tissue derived mesenchymal stem cells on wound healing, epithelization and angiogenesis in a tracheal resection and end to end anastomosis rat model. Turk Gogus Kalp Dama 2013; 21: 1010-9.

For other styles of publication or Internet articles, see http:// www.nlm.nih.gov/bsd/uniform_requirements.html

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All illustrations (photographs, drawings, graphs, etc.), not including tables, must be labeled "Figure." Figures must be submitted both in the manuscript and as separate files.

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All tables and figures must be numbered consecutively as they are referred to in the text. Please refer to tables and figures with capitalization and unabbreviated (e.g., "As shown in Figure 2…", and not "Fig. 2" or "figure 2"). The tables and figures themselves should be given at the end of the text only, after the references, not in the running text.

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Tables and figures, including caption, title, column heads, and footnotes, must not exceed 16×20 cm and should be no smaller than 8 cm in width. For all tables, please use Word's "Create Table" feature, with no tabbed text or tables created with spaces and drawn lines. Please do not duplicate information that is already presented in the figures.

Tables must be clearly typed, each on a separate sheet, and double-spaced. Tables may be continued on another sheet if necessary, but the dimensions stated above still apply.

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The Current Thoracic Surgery is a current periodical, peer-reviewed and open access official e- journal of the Turkish Society of Thoracic Surgery which its funded and published three times annually. In April, August and December.

The language of the journal is English.

The Current Thoracic Surgery is dedicated to publishing clinical research, clinical analysis, laboratory and experimental studies, editorials, invited current reviews, case reports, interesting images and "How to Do It" papers.

The journal is based on independent and unbiased double-blinded peer-reviewed principles. Only unpublished papers that are not under review for publication elsewhere can be submitted. Current Thoracic Surgery does not accept multiple submission and duplicate submission even though the previous one was published in a different language. The authors are responsible for the scientific content of the material to be published. The Current Thoracic Surgery reserves the right to request any research materials on which the paper is based.

The Current Thoracic Surgery encourages and enables academicians, researchers, specialists to publish their valuable research in branches of general thoracic surgery, thoracic disease and thoracic surgery anesthesia. The primary aim of the journal is to publish original articles with high scientific and ethical quality and serve as a good example of medical publications in the World.

The Editorial Board of the Current Thoracic Surgery and the Publisher adheres to the principles of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the US National Library of Medicine (NLM), the World Medical Association (WMA), the US Office of Research Integrity (ORI), the European Association of Science Editors (EASE), and the International Society of Managing and Technical Editors (ISMTE).

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All articles submitted for publication are strictly reviewed for their

originality,

methodology,

importance,

quality,

ethical nature and,

suitability for the journal

The Current Thoracic Surgery uses a well-constructed scheme for the evaluation process.

The overall rejection rate of the Current Thoracic Surgery is 29%.

The average time during which the preliminary assessment of manuscripts is conducted is 4 days.

The average time during which the reviews of manuscripts are conducted is 41 days.

The average time in which the article is accepted for publication is 59 days.

The entire submission process for a manuscript is completed online through the self-explanatory online submission system.. The reviewers can reach their personal pages from the same address with their own passwords.

Manuscripts that comply with the main rules of the journal are sent to at least two external reviewers, and the reviewers are asked for their opinion about the suitability of the paper for publication. The reviewed manuscripts are then re-reviewed by the Editor in Chief and the Editorial Board and a decision of rejection or acceptance is shaped.

If the reviewers have any **potential competing interests**, they must notify the editor before agreeing to review a submission.

The Current Thoracic Surgery is committed to the highest standards of **research and publication ethics**. Editors will act in accordance with the relevant international rules of publication ethics (i.e., COPE guidelines, ICMJE Recommendations, CSE White Paper on Publication Ethics, CSE White Paper on Publication Ethics, WAME resources, WMA policies and ORI) if any ethical misconduct is suspected. The Editorial Board of the Current Thoracic Surgery encourages reviewers to comment on possible research or publication misconduct such as unethical research design, duplication, plagiarism, etc.

Plagiarism is a serious problem and the most common ethical issue afflicting medical writing. Current Thoracic Surgery does not allow any form of plagiarism. In accordance with our journal policy, submitted manuscripts are screened with plagiarism software to detect instances of overlapping and similar text (iThenticate and others) at least two times (during the evaluation process and after acceptance). If the reviewers have any suspect, the editors can provide them information obtained by plagiarism screening tools.

An **approval of research protocols by an ethics committee** in accordance with international agreements ("WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (last updated: October 2013, Fortaleza, Brazil)", "Guide for the care and use of laboratory ani-

mals (8th edition, 2011)" and/or "International Guiding Principles for Biomedical Research Involving Animals (2012)" is required for all research studies. If the submitted manuscript does not include ethics committee approval, it will be reviewed according to COPE's guideline (Guidance for Editors: Research, Audit and Service Evaluations). If the study should have ethical approval, authors will be asked to provide ethical approval. If they cannot provide ethical approval, their manuscript will be rejected and also their institutions and when needed, the related bodies in their country will be informed that such studies must have ethics committee approval. If the study does not need ethics committee approval after the editorial board's review, the authors will be asked to provide an ethics committee approval or a document given by a related independent committee that indicates the study does not need ethics committee approval according to the research integrity rules in their country. If the authors provide either an approval or a document showing that ethics approval is not needed, the review process will continue. If the authors cannot provide either documents, the manuscript will be rejected. For articles concerning experimental research on humans, a statement should be included that shows informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo.

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Our reviewers are expected to check that the art icles comply with the SAGER guidelines and encourage authors to do so. Authors should use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Article titles and/or abstracts should indicate clearly what sex(es) the study applies to. Authors should also describe in the background, whether sex and/or gender differences may be expected; report how sex and/or gender were accounted for in the design of the study; provide disaggregated data by sex and/or gender, where appropriate; and discuss respective results. If a sex and/or gender analysis was not conducted, the rationale should be given in the discussion.

The Current Thoracic Surgery uses bibliographic databases and also accepts authors' suggestions to find new reviewers. The journal thanks to the reviewers and publishes the reviewer list every year in the last issue.

Besides the rutine questions given at the reviewers' comment page, the reviewers can also use the questions below, when reviewing the manuscripts:

1. Please do state if any conflict(s) of interest is present to review this manuscript.

2. Do you suspect any research or publication misconduct?

3. Does the manuscript contain significant information to justify publication?

4. Is the title of the article appropriate?

5. Does the abstract clearly and accurately describe the content of the article?

6. Is the problem significantly and concisely stated?

7. Are the methods of the study described comprehensively?

8. Is the results section clear and satisfactory?

9. Are the interpretations and conclusions justified by the results?

10. If adequate and current references were given?

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12. Are the figure/table lagends satisfactory?

13. Is it necessary to shorten/elongate the article sections?

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