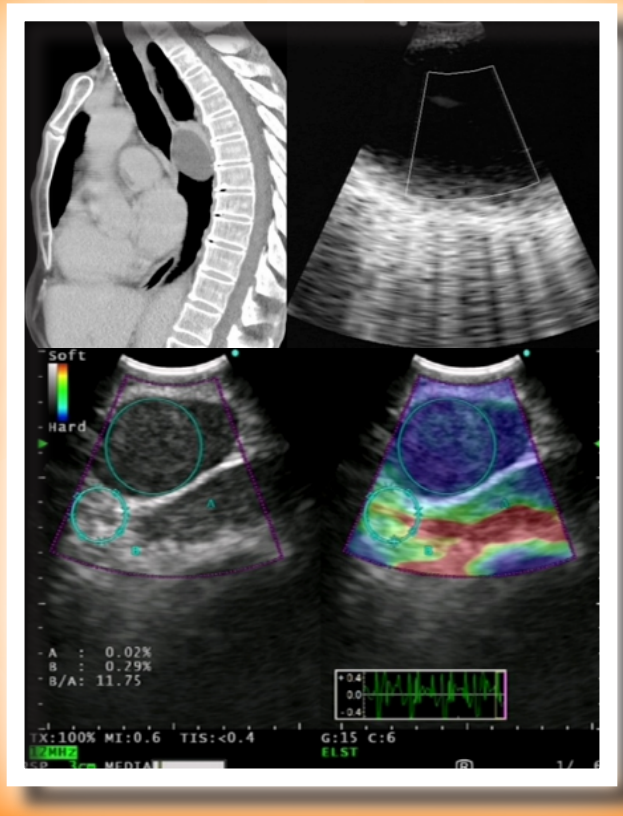
Volume 1 Number 1 December 2016

eISSN 2548-0316

CURRENT THORACIC SURGERY



Official e-journal of the Turkish Society of Thoracic Surgery

CTS

When you cite this journal, use the following abbreviation

Curr Thorac Surg

Aims and Scope

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

The Current Thoracic Surgery publishes articles in branches of thoracic surgery, thoracic surgery anesthesia and thoracic disease (lung disease, cardiac disease, esophagus disease).

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. There is no fee involved throughout the publication process.

Being a peer-reviewed journal, the manuscripts sent will be evaluated by consultants and should be appropriate for the current version of common rules indicated for biomedical manuscripts as defined by the International Committee of Medical Journal Editors (ICMJE).

The journal accepts English language manuscripts. Articles will not be accepted for evaluation if they have been published or if they are considered for publication elsewhere and if they are not prepared according to the publication rules of the journal.

Official e-Publication of:

Turkish Society of Thoracic Surgery (TSTS)

Conflict of Interest Statement

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 article.

Disclaimer

The Owner and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and options expressed do not necessarily reflect those of the Owner and Editors, neither does the publication of advertisements constitute any endorsement by the Owner and Editors of the products advertised.

For submission instructions, subscription and all other information, please visit dergipark.gov.tr

TURKISH SOCIETY OF THORACIC SURGERY

TÜRK GÖĞÜS CERRAHİSİ DERNEĞİ

Volume 1 **Number 1** **December 2016** **eISSN 2548-0316**

Editorial

Dear members of the scientific world,

The Turkish Society of Thoracic Surgery is taking a big step. We are attempting to sign on an e-journal, the "Current Thoracic Surgery", that will help us make a name for ourselves at the international scientific platform, and make an important contribution to our society in the near future.

Thoracic Surgery has become a scientific field that has found its place in today's medicine. Increased knowledge parallel to the development of technology has enabled the continuous production of information. We believe that, we need to have scientists who really produce technology rather than using the technology produced by others. Although the country is located in a difficult socio-politic region, it should be our priority to pay importance to research and development and to produce scientific work no matter what is essential. And we believe that the Turkish thoracic surgeons are ready for this task. The dynamic members of our society proceed significantly.

We provide up-to-date information, we discuss and share them by organizing congresses, scientific meetings and various activities. As well said in the idiom "Words fly away, writings remain", is a sine qua non philosophical principle to write down the findings of the scientific investigations. Many national and international scientific works from our country have been published in the literature in recent years.

Besides the official journal being published together with the Turkish Society of Cardiovascular Surgery, the "Turkish Journal of Thoracic and Cardiovascular Surgery", which is indexed by SCI-E, there was a need for a journal to be able to publish the increasing number of articles. A rigorous work was undertaken to fulfill this need and here we present you the first issue of our electronic journal that the preparations have been underway for about a year. We will try to make this journal a precious work with your academic and scientific contributions, and we will share the pride together.

It is Turkish scientists' responsibility to produce a lot higher quality work to reveal their presence in the scientific literature. As stated in the Turkish idiom "Craft is subject to compliment", appreciation of the scientific efforts is one of the primary goals of medical specialty societies. I am grateful to my colleagues and esteemed members of executive committee for their contributions to this first issue of the journal. I wish good luck and best of success to all.

Hereby, I wish a peaceful new year to all our esteemed members of the Turkish Society of Thoracic Surgery and colleagues.

Best regards,

Levent Elbeyli, MD, Professor of Thoracic Surgery

President, Turkish Society of Thoracic Surgery

Editorial

Dear Colleagues,

It is an honor for me to present you the first issue of Current Thoracic Surgery which will be a periodical, peer-reviewed and open access e- journal belonging to the Turkish Society of Thoracic Surgery.

The Current Thoracic Surgery will publish articles in branches of general thoracic surgery, thoracic diseases and thoracic surgery anesthesia, three times annually.

The Current Thoracic Surgery is dedicated to publish clinical research articles, clinical analysis articles, laboratory and experimental studies, editorials, invited current reviews, case reports, interesting images and "How to Do It" papers. Being a peer-reviewed journal, the manuscripts sent will be evaluated by consultants and should be appropriate for the current version of common rules indicated for biomedical manuscripts as defined by the International Committee of Medical Journal Editors.

Manuscripts have to be submitted through the online system for TUBİTAK ULAKBİM DergiPark at http://dergipark.gov.tr/currthoracsurg. You will be guided for uploading of the files in a few steps.

The principle aim is the exchange of knowledge by providing freely available articles on journal web site. I want to remind you that currently the journal has not been indexed in any national or international indexes. However beginning from the first issue we will suggest the journal to several indexes which are important for the visibility of the journal.

I wish you all the best in your studies in this upcoming year.

Berkant Özpolat, MD, Professor of Thoracic Surgery

Editor-in Chief

Table of Contents

Volume 1 **Number 1** **December 2016** **e-ISSN 2548-0316**

Original Articles

Case Reports

Reviews

To cite this article: Acute histopathological effects of cryotherapy on lung tissue. Yoldaş B, Çakan A, Çağırıcı U, Turhan K, Ertuğrul V, Veral A, Aşkar F. Curr Thorac Surg 2016; 1(1): 1-5

Original Article

Acute histopathological effects of cryotherapy on lung tissue

Banu Yoldaş[1a], Alpaslan Çakan[2], Ufuk Çağırıcı[2], Kutsal Turhan[2], Volkan Ertuğrul[3], Ali Veral[4], Fatma Aşkar[4]

[1]Department of Thoracic Surgery, İzmir Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital, İzmir, Turkey
[2]Department of Thoracic Surgery, School of Medicine, Ege University, İzmir, Turkey
[3]Department of Anesthesiology and Reanimation, Private Ege City Hospital, İzmir, Turkey
[4]Department of Pathology, School of Medicine, Ege University, İzmir, Turkey

ABSTRACT

Background: Cryotherapy is an actual treatment and diagnostic method in many fields of medicine. We aimed to evaluate the acute histopathological effects of cryotherapy application on lung tissue.

Materials and Methods: In this study 10 male rabbits were used. After providing single lung ventilation of the rabbits, clamshell incision was performed for exploration. Four different cryotherapy applications were performed to determine the different histopathologic changes on atelectatic and ventilated lung, also the difference between one versus two-cycle applications. After all applications, firstly, air leak was checked, then specimens were taken to analyze the acute histopathologic effects.

Results: After cryotherapy application, no air leak was detected on ventilated rabbit lung with a pressure of 30 cmH2O. There was no bleeding from lung tissue, but macroscopic parenchymal hematoma developed. The depth of necrosis in lung tissue was evaluated with histopathological analysis. In all samples, alveolar edema and congestion were observed but there was no statistical difference between the depth of necrosis regarding with different cryotherapy applications.

Conclusions: This study indicated that different applications of cryotherapy on lung parenchyma is a safe method and do not affect the depth of necrosis in a statistically significant degree.

Keywords: Experimental model; lung; cryotherapy; air leak

Corresponding Author[a]: Banu Yoldaş, MD. Department of Thoracic Surgery, İzmir Dr. Suat Seren, Chest Diseases and Surgery Training and Research Hospital, Yenişehir, İzmir, Turkey.
E-mail: banuaktin@yahoo.com

Received 10.06.2016 accepted 26.09.2016

Introduction

Cryotherapy is a method which has a usage for many organs and diseases especially for malignancies. For medically or surgically inoperable patients with lung cancer, cryotherapy is used sporadically. Recently, transbronchial cryobiopsies are getting more common in the diagnosis of interstitial lung diseases.

In this study, we aimed to evaluate air leak and acute histopathological effects on lung caused by the therapy, to guide how to use cryotherapy and adapt this method to a surgical approach.

Materials and Methods

Ten male rabbits weighing 944-1386 grams were used and the study was approved by the "Local Ethics Committee of Animal Experiments" of our hospital.

For the application, a carbon dioxide cryoprobe which provides a temperature around -40 C° at the probe tip was used. As the probe used for application on human was large for rabbit lung, a probe with a 3 mm tip diameter was obtained (Figure 1).

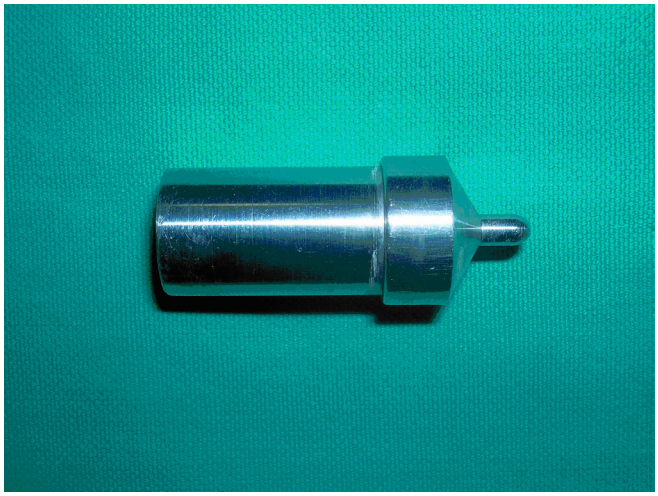


Figure 1. The probe with a 3 mm tip diameter for the application on rabbit lung.

Experimental Study Method

The induction of anesthesia was provided with ketamine (10 mg/kg) and xylazine (3 mg/kg) via 24 gauge cannula which was placed to lateral ear vein of the rabbit. After removal of the hair from the surgical site with cervical incision trachea was dissected, a transverse tracheotomy was done and intubation was provided with a 3 or 3.5 mm diameter endotracheal tube (Figure 2).

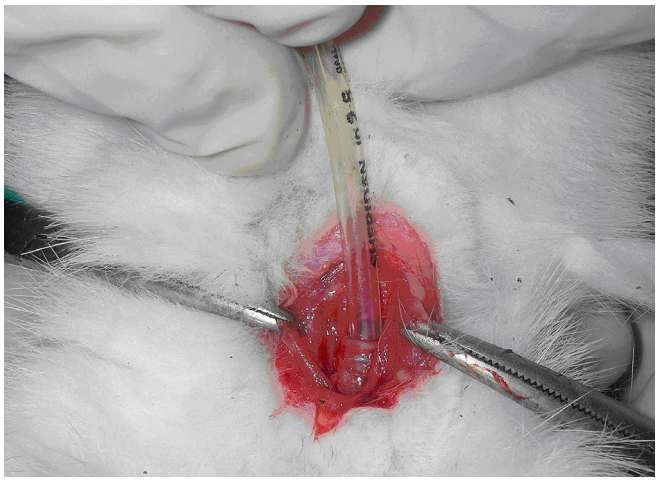


Figure 2. Intubation via cervical tracheotomy

Animals were connected to mechanical ventilator (Servo 900 C, Siemens, Sweden). Following intubation, cisatracurium was used (0.5 mg/kg) intravenously for muscle paralysis. The continuity of anesthesia was secured with ketamine and xylazine bolus infusions. The animals were ventilated with a beginning 10 cmH2O airway pressure in pressure control mode. In order to provide exposure to both hemithorax, a clamshell incision was used, and by pushing the intubation tube forward to right main bronchus single lung ventilation was achieved. First application was performed on the atelectatic lung's one lobe for a cycle (every cycle contains a freezing period of 20 seconds and a slow thawing period after) and two cycles to another lobe superficially (Figure 3).

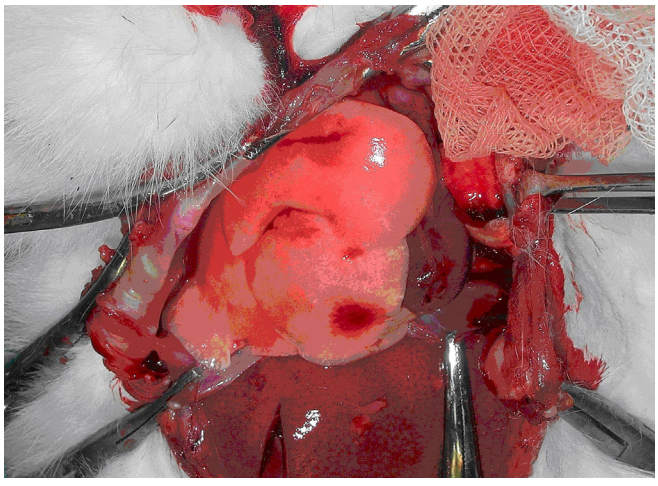


Figure 3. The macroscopic view of the hematoma on ventilated lung after cryo application.

After the thawing finished completely, thoracic cavity was filled with saline solution in order to check air leak and both lungs were ventilated with an increasing airway pressure 5 cmH20 gradually up to 30 cmH20 in

every 5 minutes. The same procedure was performed on ventilated right lung, to different lobes, as one and two cycles respectively. To summarize, one cycle cryotherapy was performed for one lobe of the atelectatic left lung (method 1), and two cycles for other lobe (method 2). On the other hand, for ventilated right lung one and two cycle therapies were performed for different lobes (method 3 and method 4 respectively). After air leak check out, lobes were resected for histopathological examination. Animals were sacrificed with high dose intravenous potassium-chloride. The resected lobes were fixed in 10% formalin solution..

Histopathological research

Four-micron sections straight to the cryotherapy application sites were obtained and they were stained with hematoxylin eosin. All the specimens were evaluated by a blinded histopathological examination. The parenchymal injury was evaluated with ocular micrometer measuring the depth of coagulation necrosis.

Statistical method

Because a few number of animals were used for the study, “two-factor analysis of variance” was used. Statistical analysis was performed using SPSS 10.0 (SPSS Inc., Chicago, IL, USA) for windows and p values less than 0.05 were considered significant.

Results

In all specimens’, after histopathological evaluation, coagulation necrosis with various levels, alveolar congestion, edema and intraalveolar hemorrhage were observed (Figure 4).

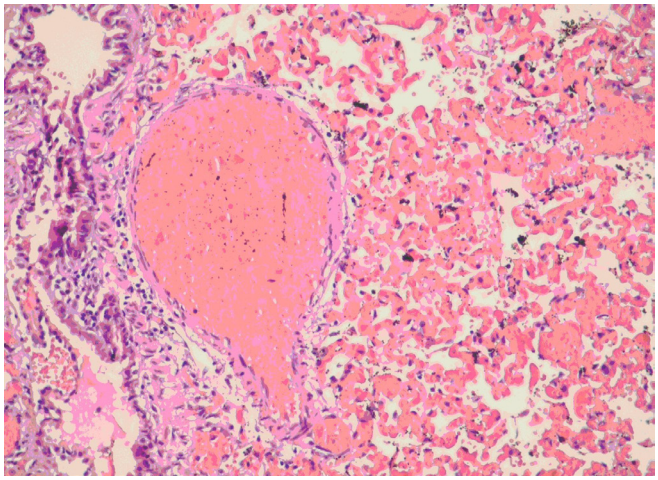


Figure 4. Alveolar congestion, edema and intraalveolar hemorrhage (hematoxylin-eosin).

The level of coagulation necrosis were evaluated on tissue samples with ocular micrometers (Table 1).

Table 1. The mean value of necrosis on the lung after cryotherapy applications

Application	Method 1	Method 2	Method 3	Method 4
Mean tissue necrosis (micron)	1931.3	1931.3	1581.6	1764.5

Air leak was not detected in any of the methods tough airway pressure was increased up to 30 cmH2O. Hemorrhage, from lung parenchyma to the pleural cavity was not seen macroscopically. Only a limited hematoma was observed in the application site.

Medium values of coagulation necrosis in atelectatic left lung was more than it was in the ventilated right lung. There was not any statistical difference between methods although the lowest value of coagulation necrosis was observed in method 3 ("one-cycle" application on ventilated lung).

Discussion

Application of cryotherapy on lung is still controversial although it has a both experimental and routine clinical application area on many organs such as prostate, kidney and liver [1-5]. Due to the specialty of lung tissue, there are two important points to be kept in mind. One is whether the application will cause air leak or not and the other is the histopathological depth of necrosis on alveolar structure? Permpongkosol et al. demonstrated the different histopathological effects of same cryotherapy protocol on kidney, liver and lung [6].

At the study of Çakan et al. comparing non-anatomic pulmonary resection via ligasure and harmonic scalpel, the maximum depth of necrosis was 731.5 micron, whereas at our study there were differences when cryotherapy was applied on parenchymal surface versus other methods and depth of necrosis was ranging between 1581-1931 microns [7].

Unlike other solid organs, there are two different options for pulmonary applications. In our study, with one lung ventilation when cryotherapy applied to both ventilated and non-ventilated lung tissue, the depth of necrosis on alveolar tissue and air leak were analysed separately. In addition, the safety of one or two cycles of cryotherapy applications were researched.

In the study of Izumi et al. comparing one and two cycles of cryotherapy on normal lung tissue in a porcine model, there was a significant air leak and hemorrhage detected additionally at the area of the lesion tripled with two cycles of cryoablation versus one cycle [8].

Wang et al. obtained successful results with computed tomography guided percutaneous cryotherapy, on patients with one or more masses that failed with previous therapies (radiation therapy, chemotherapy and /or surgery) or had nonresectable central lung cancer [9]. They inserted cryoprobes although the lung was ventilated and performed the therapy. By 6 months 86% of the treated areas were stable or smaller than the original tumor [10]. Pneumothorax due to the procedure occurred in 12% of the patients and only a few of them required tube thoracostomy.

Nowadays, in thoracic applications, cryotherapy is mostly used in endobronchial tumors. It is a treatment option for patients with an airway obstruction, alternative to laser, diathermia, photodynamic therapy and stent applications [10-16]. Cryotherapy with minimal complication ratios were reported to be a good tolerated method by Maiwant et al. [17-18]. Moorjani et al. indicated that in none of the cases, bronchial perforation or mortality was seen and highlighted the priority of the method [19].

One another usage of cryotherapy is transbronchial cryobiopsy. Although surgical biopsy is still the gold standard for diagnosis of interstitial lung diseases, transbronchial cryobiopsy is getting more common with satisfactory results [20-23]. Pneumothorax and bleeding are the most common complications [21]. Bleeding could be effectively managed in endoscopy unit as reported by Hagmeyer et al. [22].

When cryotherapy is applied directly to the parenchymal surface of lung, it causes pulmonary edema and hemorrhage. For this reason, Izumi et al. applied cryoablation for the treatment of experimentally created air leaks. Their study demonstrated that another potential application of cryotherapy was the control of air leak from dissected raw lung surfaces during lung resection [24]. In our study, cryotherapy probe was not applied inside the parenchymal tissue but on the lung surface and similarly no air leak was detected but only an intraparenchymal hematoma has occurred.

In this study, cryotherapy which comes to order nowadays with its application for cancer treatment, is demonstrated to be effective causing pulmonary hematoma and vascular thrombosis when used superficially and there was no statistical differences between different methods of applications. In conclusion, we are in the opinion that according to our results further studies are needed to investigate usage of cryotherapy.

Declaration of conflicting interests

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

Funding

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

References

1. Polascik TJ, Nosnik I, Mayes JM, Mouraviev V. Short-term cancer control after primary cryosurgical ablation for clinically localized prostate cancer using third-generation cryotechnology. Urology 2007; 70: 117-21.
2. Chin JL, Lim D, Abdelhady M. Review of primary and salvage cryoablation for prostate cancer. Cancer Control 2007; 14: 231-7.
3. Nakada SY, Jerde TJ, Warner T, Lee FT. Comparison of cryotherapy and nephrectomy in treating implanted VX-2 carcinoma in rabbit kidneys. Investig Urol 2004; 94: 632-6.
4. Janzen NK, Perry KT, Han KR, Kristo B, Raman S, Said JW, et al. The effects of intentional cryoablation and radiofrequency ablation of renal tissue involving the collecting system in a porcine model. J Urol 2007; 173: 1368-74.
5. Ng KK, Lam CM, Poon RT, Shek TW, To JY, Wo YH, et al. Comparison of systemic responses of radiofrequency ablation cryotherapy and surgical resection in a porcine liver model. Ann Surg Oncol 2004; 11: 650-7.
6. Permpongkosol S, Nicol TL, Link RE, Varkarakis I, Khurana H, Zhai QJ, et al. Differences in ablation size in porcine kidney, liver and lung after cryoablation using the same ablation protocol. Am J Roentgenol 2007; 188: 1028-32.

7. Cakan A, Yoldas B, Samancilar O, Ertugrul V, Turhan K, Cagirici U, et al. Ligasure vessel sealing system versus harmonic scalpel for sutureless non-anatomical pulmonary resections in a rabbit model. Eur Surg Res 2009; 43: 24-8.
8. Izumi Y, Oyama T, Ikeda E, Kawamura M, Kobayashi K. The acute effects of transthoracic cryoablation on normal lung evaluated in a porcine model. Ann Thorac Surg 2005; 79: 318-22.
9. Wang H, Littrup PJ, Duan Y, Zhang Y, Feng H, Nie Z. Thoracic masses treated with percutaneous cryotherapy: initial experience with more than 200 procedures. Radiology 2005; 235: 289-98.
10. Maiwand MO, Asimakopoulos G. Cryosurgery for lung cancer: clinical results and technical aspects. Technol Cancer Res Treat 2004; 3: 143-50.
11. Thurer RJ. Cryotherapy in early lung cancer. Chest 2001; 120: 3-5.
12. Mathur PN, Edell E, Sutedja T, Vergnon JM. Treatment of early stage non-small lung cancer. Chest 2003; 123: 176-80.
13. Simoff MJ. Endobronchial management of advanced lung cancer. Cancer Control 2001; 8: 337-43.
14. Vergnon JM, Schmitt T, Alamartine E, Barthelemy JC, Fournel P, Emonot A. Initial combined cryotherapy and irradiation for unresectable non-small cell lung cancer. Chest 1992; 102: 1436-40.
15. Deygas N, Froudarakis M, Ozenne G, Vergnon JM. Cryotherapy in early superficial bronchogenic carcinoma. Chest 2001; 120: 26-31.
16. Asimakopoulos G, Beeson J, Evans J, Maiwand MO. Cryosurgery for malignant endobronchial tumors: analysis of outcome. Chest 2005; 127: 2007-14.
17. Maiwand MO, Evans JM, Beeson JE. The application of cryosurgery in the treatment of lung cancer. Cryobiology 2004; 48: 55-61.
18. Maiwand MO, Zehr KJ, Dyke CM, Peralta M, Tadjkarimi S, Khagani A, et al. The role of cryotherapy for airway complications after lung and heart-lung transplantation. Eur J Cardiothorac Surg 1997; 12: 549-54.
19. Moorjani N, Beeson JE, Evans JM, Maiwand MO. Cryosurgery for the treatment of benign tracheobronchial lesions. Interact Cardiovasc Thorac Surg 2004; 3: 547-50.
20. Babiak A, Hetzel J, Krishna G, Fritz P, Moeller P, Balli T, et al. Transbronchial cryobiopsy: a new tool for lung biopsies. Respiration 2009; 78: 203-8.
21. Ganganah O, Guo SL, Chiniah M, Li YS. Efficacy and safety of cryobiopsy versus forceps biopsy for interstitial lung diseases and lung tumours: A systematic review and meta-analysis. Respirology 2016; 21: 834-41.
22. Hagmeyer L, Theegarten D, Wohlschläger J, Treml M, Matthes S, Priegnitz C, et al. The role of transbronchial cryobiopsy and surgical lung biopsy in the diagnostic algorithm of interstitial lung disease. Clin Respir J 2016; 10: 589-95.
23. Cascante JA, Cebollero P, Herrero S, Yagüe A, Echegoyen A, Elizalde J, et al. Transbronchial cryobiopsy in ILD: are we on the right path? J Bronchology Interv Pulmonol 2016; 23: 204-9.
24. Izumi Y, Tsukada N, Ikeda E, Kawamura M, Kobayashi K. Superficial contact cryoablation attenuates experimentally created lung air leakage. Cryobiology 2005; 51: 306-10.

To cite this article: Samancılar Ö, Akçam Tİ, Örs Kaya Ş, Akçay O, Ceylan KC, Sevinç S, Ünsal Ş. Bilobectomy in non-small cell lung carcinoma: an analysis of indications and outcome with a review of the literature. Curr Thorac Surg 2016;1(1):6-11.

Original Article

Bilobectomy in non-small cell lung carcinoma: an analysis of indications and outcome with a review of the literature

Özgür Samancılar[1], Tevfik İlker Akçam[2a], Şeyda Örs Kaya[1], Onur Akçay[3], Kenan Can Ceylan[1], Serpil Sevinç[1], Şaban Ünsal[1]

[1]Department of Thoracic Surgery, Dr. Suat Seren Chest Disease and Thoracic Surgery Training and Research Hospital, İzmir, Turkey
[2]Department of Thoracic Surgery, School of Medicine, Ege University, İzmir, Turkey
[3]Department of Thoracic Surgery, Karşıyaka State Hospital, İzmir, Turkey

ABSTRACT

Background: The gold standard of treatment for non-small cell lung cancer (NSCLC) is anatomic pulmonary resection. Wider resection methods may be preferred due to the size or anatomic location of the tumor. One method of choice is bilobectomy due of the anatomy of the right lung.

Materials and Methods: This study retrospectively analyzed 93 patients who were diagnosed with NSCLC and had bilobectomy, complete resection, and mediastinal lymph node dissection at our center between January 2005 and April 2013.

Results: Forty-seven patients underwent superior bilobectomy (sBL), and 46 patients underwent inferior bilobectomy (iBL). Bilobectomy was performed due to fissure invasion in 51 (58.1%) patients, internal or external bronchial tumor invasion in 31 (33.3%) patients, external bronchial lymph node invasion in six (6.4%) patients, and vascular invasion in two (2.2%) patients. The bronchial invasion-based indications were significantly higher in the iBL group compared to the fissure invasion-based indications in the sBL group ($P < 0.001$).

Conclusions: Bilobectomy leads to a substantial amount of parenchymal loss in the right lung, but it is a procedure that should be performed under the necessary conditions. It is obvious that performing bilobectomy under proper indications would result in good outcomes for lung cancer patients.

Keywords: Bilobectomy; lung cancer; treatment

Corresponding Author[a]: Tevfik İlker Akçam, MD. 6754/3 st. No:3/G Yüksek Vadi House, Karşıyaka, Postal code: 35510, İzmir, Turkey.
E-mail: tevfikilkerakcam@hotmail.com

Received 21.07.2016 accepted 20.09.2016

Introduction

The gold standard of treatment for non-small cell lung cancer (NSCLC) is anatomic pulmonary resection [1,2]. Wider resection methods may be preferred due to the size or anatomic location of the tumor. One method of choice because of the anatomy of the right lung is bilobectomy. Bilobectomy is the term used when the middle lobe lobectomy added upper or lower lobectomy in addition to the right and it was first performed by Churchill in 1933 [3]. Mid-upper lobectomy is called to bilobectomy superior or upper, mid-lower lobectomy is called to inferior or lower bilobectomy [2,3]. The present study analyzed patients who underwent bilobectomy due to non-small cell lung carcinoma at our center, and the outcome of the patients were investigated.

Materials and Methods

This study retrospectively analyzed the patients who were diagnosed with non-small cell lung cancer and had bilobectomy, complete resection, and mediastinal lymph node dissection at our center between January 2005 and April 2013. We declare that the study was performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975, as revised in 1983. The patients who had a bilobectomy due to benign pathology and the patients who had undergone a sleeve resection were excluded from the study. Data was retrospectively collected from the patient files. The parameters analyzed included gender, age, bilobectomy type, neoadjuvant therapy, histopathological type, pathological stage, postoperative complications, mortality, reason for bilobectomy, and stump closure techniques (stapler vs primary). Pathological staging was done according to the seventh TNM staging system. In the presence of mediastinal lymphadenopathy, EBUS, mediastinoscopy and/or VATS were used for staging. All patients were intubated with a double-lumen intubation tube. Complete systematic mediastinal lymph node dissection was added to the bilobectomy procedure that was performed after posterolateral thoracotomy in all patients.

Statistical Methods

The data was analyzed using the Statistical Package for the Social Sciences (SPSS) 20 software. The quantitative data was analyzed using the Kolmogorov-Smirnov test for the compatibility with normal distribution, and parametric methods were used to analyze the variables with normal distribution and homogeneous variations, and non-parametric methods were used to analyze the variables without normal distribution and homogeneous variations. Two independent groups were compared using the independent t-test and the Mann-Whitney U-test. After the main factor was controlled for quantitative data, the correlations of the variables with each other were analyzed using the partial correlation test, and the categorical data was compared using Pearson's chi-square test. The effects of the factors on mortality and lifetime were analyzed using the Kaplan-Meier method (product-limit method), and the effects of prognostic variables on lifetime according to the main factor were measures using the Cox regression analysis. Quantitative data were expressed in mean ± std. (standard deviation) and median ± IQR values in the tables. Categorical data were expressed in number (n) and percentage (%). The data were analyzed at the 95% confidence interval and $P < 0.05$ was considered significant.

Results

Among 93 patients, who had bilobectomy with the diagnosis of NSCLC, 81 (76%) were male and 12 (24%) were female, with a mean age of 60 ± 10.5 (range: 23-79 years). Forty-seven patients underwent superior bilobectomy (sBL), and 46 patients underwent inferior bilobectomy (iBL) (Table 1). Based on histopathological type, 57 (61.3%) patients were in the squamous cell carcinoma, 28 (30.1%) patients were in the adenocarcinoma, and eight (8.6%) patients were in the other NSCLC group. Patients' pathological stage were IA in 15, IB in 26, IIA in 15, IIB in 18 and III3A in 19 cases.

The patients underwent bilobectomy due to four reasons under the categories of internal or external bronchial tumor invasion, fissure invasion, external bronchial metastatic lymph node invasion, and vascular invasion. Bilobectomy was performed due to fissure invasion in 54 (58.1%) patients, internal or external bronchial tumor invasion in 31 (33.3%) patients, external bronchial lymph node invasion in six (6.4%) patients, and vascular invasion in two (2.2%) patients. In the iBL group, bilobectomy was performed due to internal and external bronchial tumor invasion in 29 patients and fissure invasion in 11 patients, and these figures were the opposite of those in the sBL group. In the sBL group, 43 patients were operated due to fissure invasion, whereas the internal and external bronchial tumor invasion was limited to two patients. The bronchial invasion-based indications were significantly higher in the iBL group compared to the fissure invasion-based indications in the sBL group ($P < 0.001$). Among those who underwent bilobectomy due to bronchial invasion, 21 patients had intermediary bronchus invasion and ten patients had middle lobe bronchus invasion. Among those who underwent bilobectomy due to fissure invasion, 43 patients had minor fissure invasion, and 11 patients had bilobectomy due to tumor invasion in the middle lobe by invading the major fissure.

Table 1. Demographics - patient distribution

		sBL (n=47)	iBL (n=46)	Total		P-value
Bilobectomy indication	Bronchial	2	29	31		< 0.001
	Fissure invasion	43	11	54		
	Lymphatic	1	5	6		0.086
	Vascular	1	1	2		0.988
N status	N0	35	28	63	0.161	
	N1	9	6	15	0.423	0.034
	N2	3	12	15	0.010	
Histopathology	Adenocarcinoma	19	9	28	0.028	
	SCC	24	33	57	0.041	0.083
	Other	4	4	8	0.975	
Complication	PAL	8	14	22	0.128	
	Pneumonia	0	2	2	0.242	
	Empyema	0	2	2	0.242	
	BPF	2	1	3	0.570	
	Atelectasis	1	3	4	0.361	0.353
	Arrhythmia	2	1	3	0.570	
	Chylothorax	0	1	1	0.309	
	PTE	2	0	2	0.157	
	SE	0	2	2	0.242	
Sex	Male	40	41	81		0.759
	Female	7	5	12		
Age		61.1 / years	58.9 / years //years			0.590
Drainage time		8.3 / days	10.3 / days			0.163

sBL: superior bilobectomy; iBL: inferior bilobectomy, N: lymph node station, SCC: squamous cell carcinoma, PAL: prolonged air leak, BPF: bronchopleural fistula, PTE: pulmonary thromboembolism, SE: subcutaneous emphysema

The mean drainage time was 9.3 ± 7.4 (range: 3-52) days in the overall group. The mean drainage time was 8.3 days in the sBL group compared to 10.3 days in the iBL group, and there was no statistically significant difference between the groups (P = 0.163). When the drainage times were compared considering bilobectomy indication, the mean time was 9.1 days due to bronchial causes, 8.8 days due to fissure-related causes, 15.2 days due to lymph node invasion, and 8.5 days due to vascular causes (P = 0.248).

Forty (43%) patients from the study group developed postoperative complications. The distribution was as follows; prolonged air leak (PAL) in 22 (23.6%) patients, atelectasis requiring bronchoscopy in four (4.3%) patients, cardiac arrhythmia in three (3.2%) patients, bronchopleural fistula in three (3.2%) patients, pneumonia in two (2.1%) patients, empyema in two (2.1%) patients, subcutaneous emphysema in two (2.1%) patients, pulmonary thromboembolism in two (2.1%) patients, and chylothorax in one (1.1%) patient. Re-thoracotomy was performed in four patients, as completion to sleeve resection in two patients, and fistula repair in one patient who developed bronchopleural fistula, and ductus ligation in one patient who developed chylothorax. Two patients died within the first postoperative month (2.1%). Pneumoperitoneum was performed in three of 22 patients who developed PAL. There were no complications in the remaining 53 patients. The bronchus closure was completed using a stapler in two and by suturing in one of three patients who developed bronchopleural fistula, whereas two patients had sBL and the other patient had iBL. Eighteen patients from the sBL group and 22 patients from the iBL group developed complications, and there was a balanced distribution between the groups (P = 0.533). Fourteen patients from the iBL group had PAL compared to eight patients from the sBL group (P = 0.128). When the development of complications was compared considering bilobectomy indication; complications were developed in 16 patients who had bilobectomy due to bronchial causes, 19 pa-

tients who were operated due to fissure crossing, three of the patients who were surgically treated due to lymphatic etiology, and two patients who had bilobectomy due to vascular causes, and there was no statistically significant difference between the groups (P = 0.168).

The mean duration of follow-up of the patients was 45.8 months (range: 1-117 months), and 56% of the patients are alive. Intraoperative mortality was not observed in the study group, but two patients died from operation-related complications within the first thirty postoperative days and considered as early mortality. For this reason, the survival calculations were made on 91 patients. As calculated using the Kaplan-Meier survival analysis, the median survival of 91 patients was 40 months and the three-year and five-year survival rates were 64.3% and 59.6%, respectively. When survival was analyzed considering the bilobectomy type, the median survival time was 37 and 41 months for superior and inferior bilobectomy, respectively, and there was no statistically significant difference in between (P = 0.324) (Figure 1). The median survival time was 37, 38, and 49 months for the patients diagnosed with adenocarcinoma, squamous cell carcinoma, and other NSCLC, respectively, and the five-year survival rate was 57.1%, 58.3%, and 75%, respectively (P = 0.687) (Table 2). When the survival of the overall group was analyzed considering lymph node (N) status, the median survival was 49 months in N0, 41 months in N1, and 33 months in N2, and the five-year survival rates were 65.9%, 47.7%, and 45.7%, respectively; there was no statistically significant difference between the groups (P = 0.236).

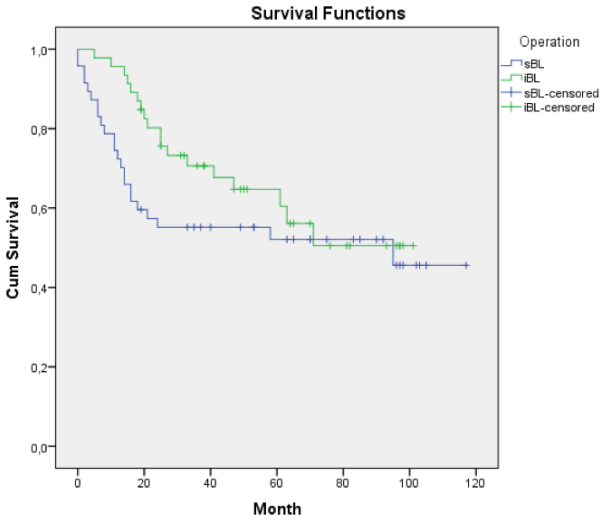


Figure 1. Survival of patients according to type of resection

Table 2. Survival rate of the patients according to resection type, histopathology and n-status

	n	Mean Survival / Months	Five years survival rates (%)	P-value
Patients	91	40	59.6	
Type of bilobectomy				
Superior	46	37	60.4	0.324
Inferior	45	41	54.4	
Histopathological type				
Adenocarcinoma	28	37	57.1	0.687
SCC	55	38	58.3	
Other	8	49	75	
N status				
N0	62	49	65.9	0.236
N1	14	41	47.7	
N2	15	33	45.7	

SCC: squamous cell carcinoma

Discussion

Bilobectomy was first performed in 1933, and the limited number of studies conducted afterwards [3,5-6]. Inferior bilobectomy was more frequent in the early studies conducted on this matter, whereas superior bilobectomy has increased in number over time. The rate of inferior bilobectomy was 65% in the series of Keller et al. [4], 86% in the series of Deneuville et al. [6], 84% in the series of Massard et al. [1], 82% in the series of Carbognani et al. [1], and 62% in the series of Kim et al. [7], whereas superior bilobectomy was performed by Icard et al. [2] at a rate of 52% in their series and similarly, at a rate of 52% by Galetta et al. [4] in their series. The numbers of iBL and sBL were close in our series, and sBL was performed in 47 (50.5%) patients and iBL was performed in 46 (49.5%) patients.

Among the most important issues that may occur after bilobectomy is the diameter mismatch between lung and pleural cavity, and the pleural and pulmonary complications caused by the remaining lung tissue not being able to fill the thoracic cavity [2,9]. In the literature, the ratio of post-bilobectomy complications varied between 35% and 49% [1,4,6], which is consistent with the ratio (43%) in our series. Several studies have demonstrated that pulmonary complications are more common in the iBL group [1,2,6]. This is attributed to the higher number of lung segments resected in iBL [2]. In the present study, the number of pulmonary complications were higher, but there were no statistical differences between two groups.

One of the most important pulmonary complications that may develop after surgical resection is prolonged air leak in non-small cell lung cancer. The study by Keller et al. stated that the limit for prolonged air leak was 14 days and reported that three patients developed prolonged air leak [5]. Deneuville et al. [6] reported prolonged air leak in ten (6.8%) patients, Kim et al. [8] reported prolonged air leak in eight (9%) patients, Massard et al. [1] reported prolonged air leak in 18 (16%) patients, and Galetta et al. [4] reported prolonged air leak in 22 (15.1%) patients. In the present study, the limit for prolonged air leak was seven days and 22 (23.6%) patients developed PAL. In the study by Massard et al. [1] a higher percentage of prolonged air leak was found in the sBL group, but did not provide any statistical information on this matter. In the present study, prolonged air leak was more common in the iBL group, however there was no statistically significant difference between the groups (P = 0.128).

Bronchopleural fistula is among the major and undesired complications that may develop after pulmonary resections [10]. The rate of incidence for bronchopleural fistula after bilobectomy varied between 0.6% and 8% [4,6]. This rate was 3% in our series. In the study by Vester et al. [11] consisting of a pulmonary resection series of 2000 diseases, nine of the patients who had bilobectomy developed BPF and the bronchial stump was closed by using sutures in all of these patients. In our series, three patients developed BPF and the bronchial stump was closed by using a stapler in two patients and by sutures in one patient. In the study by Deneuville et al. [6], all of 13 patients with BPF were from the inferior bilobectomy group, whereas the superior bilobectomy was performed on two patients and inferior bilobectomy was performed on one of the patients developing BPF in our series.

The mortality rate within the first thirty postoperative days varies from 0.97% to 6.1% in various series [1,2,5,6,8,12]. Icard et al. [2] reported that mortality varied from 3.5% to 6.1% within the first thirty postoperative days in their first series published and highlighted that the mortality within the first thirty postoperative days reduced over time. In the same study, Icard et al. [2] stated that the postoperative mortality of bilobectomies were not statistically different from lobectomies and significantly lower than pneumonectomies, based on his own experience. In our series, two (2.1%) patients died within the first 30 postoperative days due to pulmonary thromboembolism.

The literature review revealed that the five-year survival rate varied between 26% and 58% in patients undergoing bilobectomy for non-small cell lung cancer [1,2,4,6,8]. In our series, the median survival of the overall group was 40 months, and the five-year survival was 59.6%. The study by Galetta et al. [4] found that the five-year survival rate was 43% and 76.2% in patients who had superior and inferior bilobectomy, respectively, and reported a significant difference between the groups. In the present study, the five-year survival rate was 60.4% in patients from the superior bilobectomy group and 54.4% in the patients from the inferior bilobectomy group. There is no significant difference between these two groups.

The bilobectomy series in the literature revealed that, the five-year survival rate varied from 34% to 74.5% in N0 disease and this rate varied between 8% and 40% in N2 disease [2,4,8]. The study by Kim et al. [8] showed that the five-year survival rates were 62%, 35%, and 8% in N0, N1, and N2 disease, respectively, which was significant. In the present study, the median survival and five-year survival rates were 49 months and 65.9% in N0 disease, 41 months and 47.7% in N1 disease, and 33 months and 45.7% in N2 disease, respectively, and there was no statistically significant difference between the groups despite the reduced values.

As a conclusion bilobectomy leads to a substantial amount of parenchymal loss in the right lung, but it is a procedure that should be performed under the necessary conditions. The present study demonstrated that both inferior and superior bilobectomy can be performed at acceptable rates. It is obvious that performing bilobectomy under proper indications would result in good outcomes for lung cancer 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 for the research and/or authorship of this article.

References

1. Massard G, Dabbagh A, Dumont P, Kessler R, Roeslin N, Wihlm JM, et al. Are bilobectomies acceptable procedures? Ann Thorac Surg 1995; 60: 640-5.
2. Icard P, Heyndrickx M, Galateau-Salle F, Rosat P, Lerochais JP, Gervais R, et al. Does bilobectomy offer satisfactory long-term survival outcome for non-small cell lung cancer? Ann Thorac Surg 2013; 9: 1726-33.
3. Churchill ED. The surgical treatment of carcinoma of the lung. J Thorac Surg 1933; 2: 254-66.
4. Galetta D, Solli P, Borri A, Petrella F, Gasparri R, Brambilla D, et al. Bilobectomy for lung cancer: analysis of indications, postoperative results, and long-term outcomes. Ann Thorac Surg 2012; 93: 251-7.
5. Keller SM, Kaiser LR, Martini N. Bilobectomy for bronchogenic carcinoma. Ann Thorac Surg 1988; 45: 62-5.
6. Deneuville M, Regnard JF, Coggia M, Rojas-Miranda A, Dartevelle P, Levasseur P. The place for bilobectomy in bronchogenic carcinoma. Eur J Cardiothorac Surg 1992; 6: 446-51.
7. Carbognani P, Tincani G, Solli P, Galimberti A, Cattelani L, Bobbio A, et al. The bilobectomies for lung cancer. J Cardiovasc Surg 2001; 42: 421-4.
8. Kim AW, Faber LP, Warren WH, Shah ND, Basu S, Liptay MJ. Bilobectomy for non-small cell lung cancer: a search for clinical factors that may affect perioperative morbidity and long-term survival. J Thorac Cardiovasc Surg 2010; 139: 606-11.
9. Gomez MT, Jimenez MF, Aranda JL, Rodriguez M, Novoa NM, Varela G. The risk of bilobectomy compared with lobectomy: a retrospective analysis of a series of matched cases and controls. Eur J Cardiothorac Surg 2014; 16: 72-75.
10. Cerfolio RJ. The incidence, etiology, and prevention of postresectional bronchopleural fistula. Semin Thorac Cardiovasc Surg 2001; 13: 3-7.
11. Vester SR, Faber LP, Kittle CF, Warren WH, Jensik JR. Bronchopleural fistula after stapled closure of bronchus. Ann Thorac Surg 1991; 52: 1253-7.
12. 2011 ESTS Database Annual Report 2011. Available at: http://www.ests.org/ documents/ PDF/ Database silver book 2011.pdf. Accessed June 10, 2012.

Current Thoracic Surgery

To cite this article: Kocaman G, Yüksel C, Yenigün BM, Sakallı MA, Karasoy D, Özkan M, Enön S, Kayı Cangır A. Curr Thorac Surg 2016;1(1):12-15.

Original Article

Effect of tumor size on survival in pN0M0 non-small cell lung cancer patients

Gökhan Kocaman[1a], Cabir Yüksel[1], Bülent Mustafa Yenigün[1], Mehmet Ali Sakallı[1], Durdu Karasoy[2], Murat Özkan[1], Serkan Enön[1], Ayten Kayı Cangır[1]

[1]Department of Thoracic Surgery, School of Medicine, Ankara University, Ankara, Turkey
[2]Department of Statistics, Faculty of Science, Hacettepe University, Ankara, Turkey

ABSTRACT

Background: Tumor size is one of the major prognostic determinants of non-small cell lung cancer (NSCLC). In the present study, we evaluated the effect of tumor size on survival in pN0M0 NSCLC patients.

Materials and Methods: Between 1994 and 2013, 1975 NSCLC patients underwent surgery in our center. The study included 774 NSCLC patients with pathological stage N0M0, and these patients were divided into 8 groups according to tumor diameter, as follows, Group 1: 0-10 mm, Group 2: 11-20 mm, Group 3: 21-30 mm, Group 4: 31-40 mm, Group 5: 41-50 mm, Group 6: 51-60 mm, Group 7: 61-70 mm, and Group 8: > 70 mm. We aimed to evaluate the prognostic effect of tumor size on overall survival and to determine a cut-off point for tumor size.

Results: The 5 year overall survival rate for groups 1 to 8 were 85.6%, 81.3%, 68.6%, 62.2%, 55%, 54.2%, 54.3%, and 45.6%, respectively. The mean follow-up time was 43.8 months. In multivariate analysis, age, tumor size, and surgical resection type had an independent prognostic value on survival.

Conclusions: Tumor size is an independent prognostic factor for pN0M0 NSCLC patients. A tumor size of 4 cm was found to be the most suitable cut-off point for survival which may be of help in decision-making for adjuvant chemotherapy.

Keywords: Non-small cell lung cancer; tumor size; survival

Corresponding Author[a]: Gökhan Kocaman, MD. Department of Thoracic Surgery, School of Medicine, Ankara University, İbni Sina Hospital, Sıhhiye, Ankara, Turkey.
E-mail: gkhnkcmn@hotmail.com

Received 22.10.2016 accepted 5.12.2016

Introduction

Tumor size is one of the major prognostic determinants of non-small cell lung cancer. In the Eighth edition of the TNM Classification of Lung Cancer, IASLC recommended to sub classify T1 into T1a (≤1 cm), T1b (>1 to ≤2 cm), and T1c (>2 to ≤3 cm); T2 into T2a (>3 to ≤4 cm) and T2b (>4 to ≤5 cm); and reclassify T3 tumors as >5 cm to ≤7 cm and T4 tumors as >7 cm. Tumor size is a well-established prognostic factor. The statistical analysis was performed in a cohort of patients with pN0M0R0, pN0M0Rx, pNxM0R0 and cN0M0 diseases. The T descriptors within the same group were analyzed separately. There is a complex set of analysis and comparisons [1]. The best subset of patients to study the effect of tumor size on survival is pN0M0 group. By using this group, the confounding effect of nodal metastasis is removed. Another important issue is when to give adjuvant therapy in pN0 patients. In this study, we aimed to evaluate the effect of tumor size on survival in NSCLC patients with pathological stage N0M0.

Materials and Methods

This is a retrospective single center study. Between 1994 and 2013, 1975 non-small cell lung cancer patients underwent surgery in Ankara University School of Medicine Thoracic Surgery Department. We only included pN0M0 NSCLC patients. Patients with lymph node metastases, those without lymph node examination or without appropriate staging information and those with metastasis were excluded. The data of age, sex, tumor diameter, tumor histology, resection type, pathological T stage and overall survival (time between surgery and death) were recorded from the medical files. We declare that the study was performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975, as revised in 1983. The patients were divided into 8 groups according to tumor diameter, as follows, Group 1: 0-10 mm, Group 2: 11-20 mm, Group 3: 21-30 mm, Group 4: 31-40 mm, Group 5: 41-50 mm, Group 6: 51-60 mm, Group 7: 61-70 mm, and Group 8: >70 mm. We used Kaplan-Meier method with log-rank test for univariate analysis and Cox regression analysis (forward stepwise) for multivariate survival analysis. SPSS version 15.0 was used for statistical analysis. The statistical significance level of P was determined as ≤ 0.05.

Results

The analysis included 774 patients (87.2% male) with a mean age of 60.4 years (33-84 years).

The distribution of the patients according to tumor size was as follows, Group 1: 24 (3.1%), Group 2: 119 (15.4%), Group 3: 178 (23%), Group 4: 140 (18.1%), Group 5: 110 (14.2%), Group 6: 83 (10.8%), Group 7: 50 (6.4%), and Group 8: 70 (9%) patients. The tumor types of the patients were adenocarcinoma [374 (48.3%)], squamous cell carcinoma [393 (50.78%)] and other cell types [7 (0.9%)]. Of the patients, 522 (67.4%) underwent lobectomy, 162 (20.9%) pneumonectomy and 90 (11.63%) sublobar resection. The characteristics of the patients are summarized in Table 1.

Table 1. Patient characteristics

Variable	Number (%)
Age (years)	
≤65	535 (69.1)
>65	239 (30.8)
Sex	
Female	99 (12.8)
Male	675 (87.2)
Tumor diameter group	
1	24 (3.1)
2	119 (15.4)
3	178 (23)
4	140 (18.1)
5	110 (14.2)
6	83 (10.8)
7	50 (6.4)
8	70 (9)
Histology	
Adenocarcinoma	374 (48.3)
Squamous cell carcinoma	393 (50.7)
Other	7 (0.9)
Resection type	
Lobectomy	522 (67.4)
Pneumonectomy	162 (20.9)
Sublobar	90 (11.6)
Pathological T stage	
T1a	126 (16.2)
T1b	145 (18.7)
T2a	238 (30.7)
T2b	113 (14.6)
T3	130 (16.8)
T4	22 (2.8)

The 5 year overall survival rate for groups 1 to 8 were 85.6%, 81.3%, 68.6%, 62.2%, 55%, 54.2%, 54.3%, and 45.6%, respectively (Figure 1). Mean follow-up time was 43.8 months and median follow-up time was 43 months. Pairwise comparison between the groups for survival showed that survival was significantly longer in Group 2 than that in Group 3 (P = 0.036); the other pairwise comparisons revealed no significant difference; Group 1 vs. Group 2 (P = 0.853), Group 3 vs. Group 4 (P = 0.206), Group 4 vs. Group 5 (P = 0.088), Group 5 vs. Group 6 (P = 0.698), Group 6 vs. Group 7 (P = 0.387), and Group 7 vs. Group 8 (P = 0.305). In multivariate analysis, age, tumor diameter and resection type were found to be independent prognostic factors. Using Group 1 as reference, hazard ratios showed an increased risk for mortality, significance beginning with Group 5. As seen in Table 2 Group 3 has 1.429 and Group 4 has 2.144 times increased risk for mortality over Group 1 which are found statistically insignificant (P = 0.409, P = 0.079) but Group 5, 6, 7 and 8 have 2.910, 2.841, 2.753, 3.878 times increased risk for mortality over Group 1 and all of them are statistically significant (P = 0.015, P = 0.019, P = 0.027, P = 0.002 respectively). For resection types while pneumonectomy and lobectomy have a smiliar risk for mortality (HR = 1.045, P = 0.781), sublobar resection has 2.711 times increased risk for mortality over lobectomy (P = 0.000). We also classified patients in two groups according to tumor diameter as Group 1: ≤4 cm and Group 2: >4 cm, and found that the survival difference between the two groups was statistically significant (P = 0.000) (Figure 2).

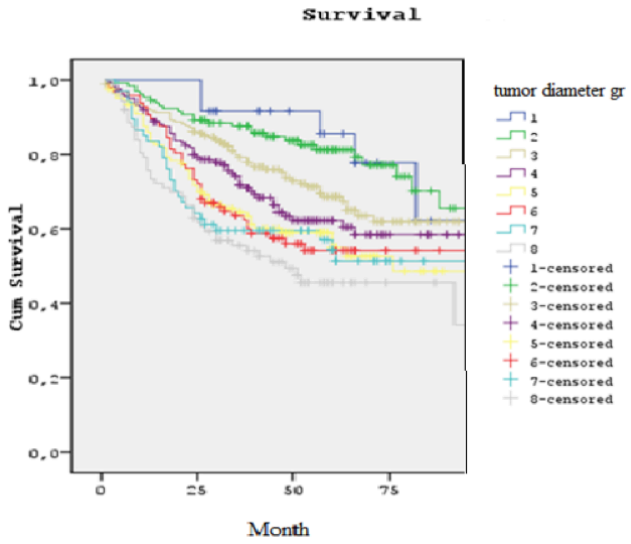


Figure 1. Survival according to tumor diameter groups

Table 2. Multivariate analysis of age, tumor groups and resection types

	Hazard ratios (%95 CI)	P-value
Age		0.043
Group 1	1 (reference)	
Group 2	0.927 (0.381-2.255)	0.868
Group 3	1.429 (0.612-3.333)	0.409
Group 4	2.144 (0.915-5.024)	0.079
Group 5	2.910 (1.234-6.860)	0.015
Group 6	2.841 (1.187-6.799)	0.019
Group 7	2.753 (1.121-6.758)	0.027
Group 8	3.878 (1.620-9.284)	0.002
Lobectomy	1 (reference)	
Pneumonectomy	1.045 (0.767-1.423)	0.781
Sublobar resection	2.711 (1.946-3.778)	0.000

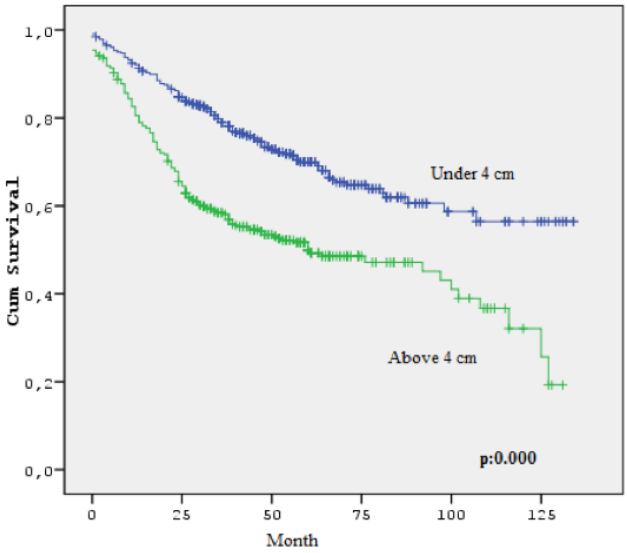


Figure 2. Survival according to tumor diameter (≤4 cm / >4 cm)

Discussion

Tumor size has an important effect on prognosis especially for node negative tumors [2]. In the Eight Edition of IASLC TNM Lung Cancer Staging Project, Rami Porta et al. [1] reported that 5 year survival rates of p N0M0 NSCLC patients with a tumor size 0.1-1 cm, 1.1-2 cm, 2.1-3 cm, 3.1-4 cm, 4.1-5 cm, 5.1-6 cm, 6.1-7 cm were 91%, 86%, 81%, 73%, 66%, 63%, and 58% respectively. Although we found a lower survival rates in the present study, we observed a similar decreasing trend with increasing tumor size.

In our study, survival was significantly longer in Group 2 in comparison to that in Group 3 (P = 0.036). This is the 2 cm cut-off point which is used for sublobar resection [3,4]. Our study also showed that sublobar re-

section has a negative effect on survival compared with lobectomy in multivariate analysis (P = 0.000). These two findings cannot be combined in this study, but it seems that they are important for selecting surgical procedure also for early stage lung cancer.

In multivariate analysis, age, tumor size and surgical resection type have independent prognostic value on survival. When Group 1 was used as reference, we observed that, beginning with group 5 (41-50 mm), hazard ratios showed a significant increasing trend, and also survival difference between the groups with a tumor size ≤4cm and >4 cm was significant, showing that a tumor size of 4 cm seems to be a critical threshold. In the earlier series [5,6] this critical threshold was reported to be 5 cm but in the eight edition of TNM Rami Porta et al. [1] found 3 cm as the most significant cut-off point for T descriptor. Zhang et al. [7] studied similar patient groups and found similar results in multivariate analysis. This finding may show that adjuvant chemotherapy may be beneficial in pN0M0 NSCLC patients with tumors greater than 4 cm in size [8-10].

There are some limitations for this study. First as a prognostic factor on N0M0 patients, tumor extension is not excluded in this study, so it may be a confounding factor on survival analysis. Second, information on adjuvant chemotherapy was not available for this study.

In conclusion, for pN0M0 NSCLC patients, tumor size is an independent prognostic factor. As in the new TNM classification 1 cm increments in tumor size show a good correlation with survival. A tumor size of 4 cm is a significant cut-off point for survival which may help in giving adjuvant chemotherapy decision for N0M0 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 for the research and/or authorship of this article.

References

1. Rami-Porta R, Bolejack V, Crowley J, Ball D, Kim J, Lyons G, et al. IASLC Staging and Prognos¬tic Factors Committee, Advisory Boards and Participating Institutions. The IASLC lung cancer staging project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol 2015; 10: 990-1003.
2. Zhang J, Gold AK, Lin HY, Swisher SG, Xing Y, Lee JJ, et al. Relationship between tumor size and survival in non-small cell lung cancer (NSCLC): an analysis of the surveillance, epidemiology, and end results (SEER) registry. J Thorac Oncol 2015; 10: 682-90.
3. Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K, Tsubota N. Radical sublobar resection for small-sized non–small cell lung cancer: A multicenter study. J Thorac Cardiovasc Surg 2006; 132: 769-75.
4. Sihoe ADL, Van Schil P. Non-small cell lung cancer: When to offer sublobar resection. Lung Cancer 2016; 84: 115-20.
5. Takeda S-i, Fukai S, Komatsu H, Nemoto E, Nakamura K, Murakami M. Impact of large tumor size on survival after resection of pathologically node negative (pN0) non-small cell lung cancer. Ann Thorac Surg 2005; 79: 1142-6.
6. Cangır AK, Kutlay H, Akal M, Güngör A, Özdemir N, Akay H. Prognostic value of tumor size in non-small cell lung cancer larger than five centimeters in diameter. Lung Cancer 2004; 26: 325-31.
7. Zhang Y, Sun Y, Chen H. Effect of tumor size on prognosis of node-negative lung cancer with sufficent lymph node examination and no disease extension. Onco Targets and Therapy 2016; 9: 649-53.
8. Speicher PJ, Gu L, Wang X, Hartwig MG, D'Amico TA, Berry MF. Adjuvant chemotherapy after lobectomy for T1-2N0 non-small cell lung cancer: are the guidelines supported? J Natl Compr Canc Netw 2015; 13: 755-61.
9. Malhotra J, Mhango G, Gomez JE, Smith C, Galsky MD, Strauss GM, et al. Adjuvant chemotherapy for elderly patients with stage I non-small-cell lung cancer ≥4 cm in size: an SEER-Medicare analysis. Ann Oncol 2015; 26: 768-73.
10. Strauss GM, Herndon II JE, Maddaus MA, Johnstone DW, Johnson EA, Harpole DH, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non–small cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008; 26: 5043-51.

Current Thoracic Surgery

To cite this article: Kutluk AC, Kocatürk CI, Akın H, Bedirhan MA, Ceritoğlu A, Hatipoğlu M, Karapınar K, Saydam Ö. Curr Thorac Surg 2016; 1(1): 16-20.

Original Article

Pulmonary sequestration: is it fraught to operate without the diagnosis?

A. Cevat Kutluk[a], Celalettin İ. Kocatürk, Hasan Akın, M. Ali Bedirhan, Altan Ceritoğlu, Merve Hatipoğlu, Kemal Karapınar, Özkan Saydam

Department of Thoracic Surgery, Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital, Istanbul, Turkey.

ABSTRACT

Background: Pulmonary sequestration is defined as nonfunctional lung tissue without a normal tracheobronchial tree that is supplied by an aberrant systemic artery. The awareness of the preoperative diagnosis could be very crucial for the safety of the operation.

Materials and Methods: We retrospectively reviewed the records of 16 patients who underwent resection for pulmonary sequestration between 2006-2016. Nine of 16 cases (56%) were female, and the mean age of the patients was 38.5 ± 9.9 years. Fiberoptic bronchoscopy and standard computed thorax tomography were performed for diagnostic work-up in all cases. The patients were divided into 2 groups based on the presence (Group A) or abscence (Group B) of the preoperative diagnosis.

Results: The most common presenting symptoms were cough and expectoration. Preoperative diagnosis of the sequestration was obtained in only 5 patients (31%). Bronchiectasis was the most common cause of false diagnosis, followed by hydatid disease, malignancy, and aspergillosis. Left-sided and intrapulmonary locations were dominant with 12 (75%) and 13 (81%) cases, respectively. Lobectomy was the most common type of surgical resection (75%) and thoracic aorta was the source of aberrant artery in 87% of the patients. Patients in group A were younger. Though intralobar and extralobar types were equally distributed in both groups, all cases in group B had intralobar type. The mean operation time, blood loss, the amount of drainage, and the hospital stay were all insignificantly longer in group B patients. Five of the 6 morbidities occured in group B patients, but the difference was not statistically significant. No mortality occured.

Conclusions: Surgical resection provides definitive management, and is usually reserved for the patients with symptoms. Facilities for a definitive diagnosis should be performed in every case, because, although insignificant, the rate of morbidity is higher in the patients without a definitive diagnosis. Further studies concerning of more patients are required to obtain more comprehensive results.

Keywords: Pulmonary sequestration; lobectomy; diagnosis; bronchiectasis

Corresponding Author[a]: A. Cevat Kutluk, MD. Department of Thoracic Surgery, Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital, Zeytinburnu, İstanbul, Turkey.
E-mail: dralikutluk@gmail.com

Received 8.11.2016 accepted 10.12.2016

Introduction

Pulmonary sequestration (PS) is defined as nonfunctional lung tissue without a normal tracheobronchial tree that is supplied by an aberrant systemic artery [1]. It accounts for 0.15-6.4% of all congenital pulmonary malformations [2]. Despite the development of new diagnostic tools like computed tomographic angiography or digital subtraction angiography, the rate of incorrect diagnosis of PS has been reported to be nearly 60% [3]. The correct diagnosis of PS before surgery provides the surgeon to plan the operation, and prevents the unpredictable hemorrhage from the aberrant artery. Failure to diagnose and treat this condition adequately can lead to reccurent pneumonia and even severe hemoptysis. Surgical resection provides definitive management and is usually reserved for patients with symptoms.

Materials and Methods

We retrospectively reviewed the records of 16 patients who underwent resection for PS at our hospital between 2006-2016. A thorough physical examination was performed, and the signs and symptom of the all patients were recorded. We declare that the study was performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975, as revised in 1983.

All cases had chest X-ray, compturized thorax tomography (CT), routine blood chemistry analysis, and pulmonary function tests.

CT-guided transthoracic aspiration biopsy and indirect hemagglutination tests were performed for solid and cystic lesions, respectively. A positron emission tomography was performed in case of the suspicion for malignancy. Computer tomographic angiography was performed in cases when PS suspicion was quite high. To evaluate the endobronchial anatomy fiberoptic bronchoscopy was performed in all cases. A wedge resection or biopsy from the lesion was performed for for patients. Sputum culture and antibiogram tests directed to appropriate antibiotics.

All surgical procedures, either thoracotomy or video-assisted thoracic surgery (VATS), were performed under single lung ventilation in a posterolateral position. As for thoracotomy, serratus anterior muscle sparing tecnique was preferred. A utility incision and a 10 mm incision for camera port were used for VATS approach. The aberrant artery to the sequestered lobe was dissected carefully, and was either sutured ligated or cut with a stapling device. All cases stayed in the intensive care unit at the day of the operation, and the pain management was achived by patient controlled analgesia.

The patients were divided into 2 groups based on the presence (Group A) or abscence (Group B) of the preoperative diagnosis. Group A consisted of 6 cases with definite diagnosis, and group B without diagnosis(ten cases). Statistical analysis was performed on patients' age, gender, symptom, lesion localization, arterial supply, type of resection, operation time, amount of blood loss, amount of drainage, drainage time, hospital stay, and complications. The data are expressed as mean values ± standard deviation or percentage. Mann Whitney U and Ki square tests were used for comparing the groups. Data were analysed using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA) and SPSS version 20.0 software (SPSS,Inc., Chicago, IL, USA).

Results

Nine of 16 (56%) cases were female, and the mean age of the patients was 38.5 ± 9.9 (range 22-56). The most common presenting symptoms were cough and expectoration. Left-sided and intrapulmonary locations were dominant with 12 (75%) and 13 (81%) cases, respectively. Lobectomy was the most common surgical type of resection with 12 patients (75%), and one of them was performed via VATS approach. Except for 2 cases, all sequestered lung tissue were supplied by thoracic aorta. The mean operation time was 148.25 ± 39.86 min, and was longer in the patients undegoing lobectomy. The clinical characteristics of the patients were given in Table 1.

For diagnostic work-up, fiberoptic bronchoscopy and standard computed thorax tomography were performed in all cases. Additional diagnostic tools were listed in Table 2. Preoperative diagnosis of PS was reached in only 5 patients (31%). Bronchiectasis was the most common false diagnosis which was followed by hydatid disease, malignancy, and aspergillosis (Figure 1).

The patients in group A were younger than group B. Though intralobar and extralobar types were disributed equally between the groups, all cases in group B had intralobar type. The mean operation time, blood loss, the amount of drainage, and the hospital stay were all longer in group B, compared to group A. None of the differences between these 2 groups reached significance due to small number of patients in the groups (Table 3).

Six of 16 patients (37.5%) developed complications after the operation. The most severe complication was bronchopleural fistula seen after left lower lobectomy. The patient was treated with tube thoracostomy and fistula was closed on 12th day of the operation. Other complications included hemmorhage requiring thoracotomy, pleural effusion necessitating drainage with pleurocan (8-10F, B. Braun, Melsungen, Germany), and wound infection treated by antibiotics. Five of the 6 morbidity occured in group B patients, but the difference was not statistically significant. No mortality occured.

Table 1. Clinical characteristics of all patients	
Variables	n (%)
Age	38.5
Sex	
Female	9 (56%)
Male	7 (44%)
Symptoms	
Cough	12 (%75)
Expectoration	9 (%56)
Hemoptysis	2 (%13)
Chest pain	1 (%6)
Pneumonia	3 (%19)
Asymptomatic	4 (%25)
Localisation	
Left Lower lobe	12 (75%)
Right Lower lobe	4 (25%)
Sequestration type	
Intralobar	13 (81%)
Extralobar	3 (19%)
Surgical approach	
Lobectomy	12 (75%)
Wedge resection	3 (19%)
Segmentectomy	1 (6%)
Feeding artery	
Thoracal Aorta	14 (87%)
Abdominal Aorta	2 (13%)
Operation time (min)	148.25
Blood loss (mL)	223.43
Amount of drainage (mL)	388.43
Drainage time (days)	3.8
Hospital stay (days)	6
Morbidity	6 patients (37%)
Bronchopleural fistula	1
Hemorrhage	1
Pneumonia	1
Empyema	1
Pleural effusion	1
Wound infection	1

Table 2. Diagnostic tools performed for all patients	
Diagnostic methods	n (%)
CT-guided TTIA	4 (25%)
Serology (Indirect hemagglutination)	2 (12.5%)
PET-CT	2 (12.5%)
Fiberoptic bronchoscopy	16 (100%)
CT angiography	3 (19%)
Intraoperative frozen section analysis	4 (25%)

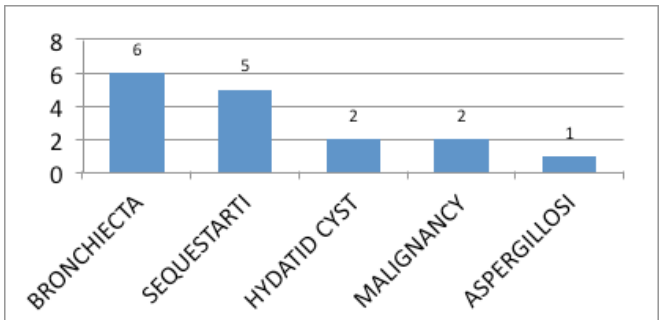


Figure 1. Distribution of preoperative diagnosis

Table 3. The comparison of clinical features of patients with definite preoperative diagnosis and without diagnosis.			
	Group A	Group B	P
Age	34.8	40.7	0.18
Localisation	5	7	0.50
Left lower lobe	1	3	
Right lower lobe			
Sequestration type	3	10	0.12
Intralobar	3	0	
Extralobar			
Feeding artery	6	8	0.37
Thoracal aorta	0	2	
Abdominal aorta			
Operation time (min.)	133.3	157.2	0.36
Blood loss (mL)	148.3	268.5	0.42
Amount of drainage (mL)	344	415	0.41
Drainage time (days)	3.1	4.2	0.82
Hospital stay (days)	5.6	6.2	0.87
Morbidity	1	5	0.21

Discussion

PS is a rare congenital malformation of the lower respiratory tract which is characterized by a solitary non-functioning mass of lung tissue lacking communication with the tracheobronchial tree and arterial blood from the systemic circulation instead of the pulmonary circulation [4]. Though it is first reported by Huber in 1877, Pryce named it as sequestration in 1946 [5]. PSs are divided into two subgroups: intralobar pulmonary sequestration (ILS) and extralobar pulmonary sequestration (ELS). ILS is the more common form and is contained within the normal lung parenchyma, while ELS is separated from the normal lung and has its own visceral pleura [6].

The diagnosis of PS was reached in only 5 (31%) of patients. The high rate of bronhiectasis and other infectious diseases like hydatid disease and aspergillosis in our country, and the possibility of malignancy in 2 cases might be the reasons for this relatively low rate of preoperative diagnosis. Moreover one case underwent resection due to massive hemoptysis.

The ability of clearly identifying the aberrant artery to the sequestered lung tissue made the digital subtraction angiography to be the gold standard for the diagnosis of pulmonary sequestration [7]. Nevertheless it is an invasive and radiation-associated procedure that requires hospitalization. In recent years, safer alternatives to digital subtraction angiography, including CT angiography and magnetic resonance imaging (MRI) have proved to be equally effective and less invasive imaging techniques [8]. We performed CT angiography in 5 cases, and identified the aberrant artery to the sequestered lung parenchyma (Figure 2). The clinical findings and thorax CT's of these cases were strongly suggestive for PS. Though the source of the aberrant artery may be any systemic artery, but in more than 80% of the cases, thoracic aorta is the origin [9,10]. Moreover finding of anomalous systemic arterial supply to basal segments of the lung does not always indicate PS [11]. Sometimes these aberrant arteries develop aneurysmatic dilatation, and cause severe hemoptysis and hemothorax [12-14].

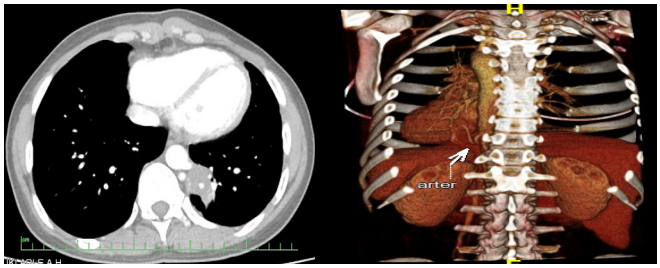


Figure 2. Thorax CT and CT angiography demonstrating 4 cm opacity in the left lower lobe (IPS) and feeding artery from the descending aorta.

In a recent study, Sun et al. [9] reported that the definitive diagnosis rate of PS before the surgery was 27 out of 72 cases (37.5%). CT angiography was performed in all 27 cases, and 3 of them underwent digital subtraction angiography (DSA) as well. All 5 ELS patients were not diagnosed with PS before surgery in that series. One of the largest series in the literature was reported by Wei et al. [3]. The total number of patients with incorrect diagnosis was 713 of 2625 cases (27%). Unlike our series the main CT appearances of these patients were mass lesions (49%) and cystic lesions (28%). The rate of misdiagnosis of PS as pulmonary cyst and lung cancer were 36.19% and 21.04%, respectively. Contrary to our series (37%) only 15% of patients of that series misdiagnosed as PS. Another recent study from our country reported that only 4 of 11 cases (36%) had the diagnosis of PS, very similar to our results [15]. Contrary to this study, Gezer et al. [1] reported a very low rate (about 10%) of correct diagnosis. They attributed this low rate of correct diagnosis to the study period which was from 1982 to 2006. The authors stressed that CT was not available in the earlier period of the study.

Despite the many studies with low rates of correct diagnosis of PS in the literature, Kestenholz et al. [16] reported 100% of correct diagnosis with 14 cases. The authors stated that the feeding artery was shown with CT scan, and additionally 3 cases had angiography and one had MRI-angiography. Halkic et al. [17] reported one of the highest rate (about 80%) of correct diagnosis. They performed angiography in 20 of 26 patients who had chest X-rays evoking the diagnosis of PS.

In addition to series, there are many case reports of PS in the literature. In those case reports the clinical picture of PS may mimic many diseases, such as hydatid disease, mediastinal mass or even malignacy [18,19]. More interestingly, there are some case reports in which adenocarcinoma was detected in the sequestered lobe [20].

The usual treatment is lobectomy or segmentectomy for ILS, wedge resection and for ELS. The surgical approach extends from open thoracotomy to minimal invasive procedures like VATS or robotic lobectomy. During the resection, the initial step is to identify the aberrant artery which is often localised in the pulmonary ligament (Figure 3). The dissection and finding the aberrant artery is usually challenging because of the adhesions and fibrotic tissue that developed due to previous infections. It is prudent to search for the aberrant artery otherwise inadvertent injury and massive hemorrhage might be unavoidable. Saxxena et al. [21] suggested embolization of the aberrant artery to avoid a catastrophy.

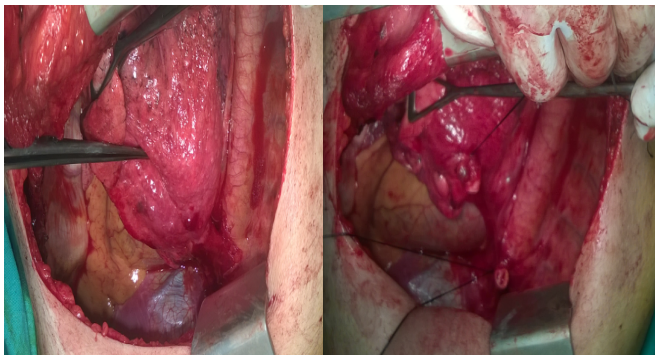


Figure 3. The operative view demonstrating ELS and division of the feeding artery originating from the descending aorta.

As a conclusion, the diagnosis of sequestration might sometimes be very difficult due to its rareness and inappropriate diagnostic methods. It should be kept in mind that, thorax CT's of the young adults, especially with symptoms of infectious states, should be carefully checked for a possible aberrant artery to the lung tissue. If neccessary, CT angiography should be performed to define the possible source of the feeding artery. Despite the difficulties

such as adhesions and inflammation, which might cause challenges in finding the feeding artery and other hilar structures, surgical resection whether performed by open thoracotomy or minimal invasive approach is quite safe in experienced thoracic centres. Facilities for a definitive diagnosis should be performed in every case, because, although insignificant, the rate of morbidity is higher in patients without a definitive diagnosis. Our study consisted of less number of patients, and was retrospective in nature. These two points are the weakness of this study. Further studies concerning of more patients are required to obtain more comprehensive results.

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.

References

1. Gezer S, Taştepe I, Sirmali M, Fındık G, Türüt H, Kaya S, et al. Pulmonary sequestration: a single-institutional series composed of 27 cases. J Thorac Cardiovasc Surg 2007; 133: 955-9.
2. Corbett HJ, Humphrey GM. Pulmonary sequestration. Paediatr Respir Rev 2004; 5: 59-68.
3. Wei Y, Li F. Pulmonary sequestration: a retrospective analysis of 2625 cases in China. Eur J Cardiothorac Surg 2011; 40: e39-e42.
4. Genc O, Gurkok S, Dakak M, Gozubuyuk A, Ozkan M, Caylak H. Pulmonary sequestration and surgical treatment. Asian Cardiovasc Thorac Ann 2006; 14: 3-6.
5. Pryce DM. Lower lobe accessory pulmonary artery with intralobar sequestration of lung: report of 7 cases. J Pathol 1946; 58: 457-67.
6. Savic B, Birtel FJ, Tholen W, Funke HD, Knoche R. Lung sequestration: report of seven cases and review of 540 published cases. Thorax 1979; 34: 96-101.
7. Franco J, Aliaga R, Domingo ML, Plaza P. Diagnosis of pulmonary sequestration by spiral CT angiography. Thorax 1998; 53: 1089-92.
8. Yue SW, Guo H, Zhang YG, Gao JB, Ma XX, Ding PX. The clinical value of computer tomographic angiography for the diagnosis and therapeutic planning of patients with pulmonary sequestration. Eur J Cardiothorac Surg 2013; 43: 946-51.
9. Sun X, Xiao Y. Pulmonary sequestration in adult patients: a retrospective study. Eur J Cardiothorac Surg 2015; 48: 279-82.
10. Osaki T, Kodate M, Takagishi T, Nomi M, Murakami J, Yamamoto H. Unique extralobar sequestration with atypical location and aberrant vessels. Ann Thorac Surg 2010; 90: 1711–2.
11. Gonca C, Hamzayev E, Atasoy C, Enon S. Anomalous systemic arterial supply to normal basal segments of the left lung without sequestration. Eur J Cardiothorac Surg 2015; 47: 578.
12. Shyam S, Sagar A, Sureka J, Jakkani RK. An unusual case of a giant aneurysm of an aberrant systemic artery supplying a pulmonary sequestration. Eur J Cardiothorac Surg 2012; 42: 592.
13. Fabre D, Rohnean A, Fadel E, Dartevelle PG. Giant aneurysmal dilation of an intralobar pulmonary sequestration artery. Eur J Cardiothorac Surg 2009; 36: 413-4.
14. Hofman FN, Pasker HG, Speekenbrink RGH. Hemoptysis and massive hemothorax as presentation of intralobar sequestration. Ann Thorac Surg 2005; 80: 2343-4.
15. Arslan E. Pulmonary sequestration with different clinical and radiological findings. Turk Gogus Kalp Dama 2013; 21: 110-3.
16. Kestenholz PB, Schneiter D, Hillinger S, Lardinois D, Weder W. Thoracoscopic treatment of pulmonary sequestration. Eur J Cardiothorac Surg 2006; 29: 815-8.
17. Halkic N, Cuenoud PF, Corthesy ME, Ksontini R, Boumghar M. Pulmonary sequestration: a review of 26 cases. Eur J Cardiothorac Surg 1998; 14: 127-33.
18. Aydin Y, Ogul H, Altuntas B, Eroglu A. Pulmonary sequestration mimicking a hydatid cyst. Eur J Cardiothorac Surg 2015; 48: 514.
19. Sippel JM, Ravichandran PS, Antonovic R, Holden WE. Extralobar Pulmonary Sequestration Presenting as a Mediastinal Malignancy. Ann Thorac Surg 1997; 63: 1169-71.
20. Simoglou C, Lawal LA. Adenocarcinoma in pulmonary sequestration: a case report and literature review. Asian Cardiovasc Thorac Ann 2015; 23: 1119-20.
21. Saxxena P, Marshall M, Ng L, Sinha A, Edwards M. Preoperative embolization of aberrant systemic artery in sequestration of lung. Asian Cardiovasc Thorac Ann 2011; 19: 357-9.

To cite this article: Tokur M, Demiröz ŞM, Sayan M, Tokur N, Arpağ H. Chest wall deformities and coincidence of additional anomalies, screening results of the 25.000 Turkish children with the review of the literature. Curr Thorac Surg 2016;1(1):21-27.

Original Article

Chest wall deformities and coincidence of additional anomalies, screening results of the 25.000 Turkish children with the review of the literature

Mahmut Tokur[1], Şevki Mustafa Demiröz[2a], Muhammet Sayan[1], Naime Tokur[3], Hüseyin Arpağ[4]

[1]Department of Thoracic Surgery, School of Medicine, Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Turkey
[2]Department of Thoracic Surgery, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey
[3]Department of Pediatrics, Necip Fazıl City Hospital, Kahramanmaraş, Turkey
[4]Department of Pulmonary Medicine, School of Medicine, Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Turkey

ABSTRACT

Background: The main subtypes of chest wall deformities are pectus excavatum (PE) and pectus carinatum (PC). Although these are not life threatening diseases, some functional or physico-social disabilities due to the abnormal chest wall structure require treatment. The main stem of the treatment is surgical correction. Since the beginning of the 20th century various surgical techniques were introduced. In the last few decades some minimally invasive surgical techniques were also described. In the English literature many reports suggest that the vast majority of these abnormalities are PE. But in most of the reports patient groups consist of hospital admissions. The real frequency of this group of disease is controversial.

Materials and Methods: In this report, a wide field study was designed to find the real frequency of the chest wall diseases. Total of 25117 children between 6-11 years of age were visited in the elementary schools of Kahramanmaraş. The team members were a thoracic surgeon, a pulmonologist and a pediatrician.

Results: A careful physical examination revealed that a total of 255 patients had different degrees of chest wall deformity. We found that PC (90.58%) was the most frequent type of deformity in contrast with the previous reports suggesting PE as the most frequent type. In our results only 5.49% of the patients had PE and 3.93% of the patients had mixed type PE+PC. The most frequent ECG abnormality seen in 49 cases (19% of cases with deformity) was a negative T wave on V1 derivation and a biphasic T wave configuration on V1-V2 derivations. 8 patients (3.13%) had concomitant scoliosis and 6 patients (%2.35) had different degrees of cardiomegaly.

Conclusions: The real frequency of chest wall deformities is an enigma. When PE patients themselves or their family notice the abnormality, they may consider it as a big health problem and admit to a healthcare unit. But in contrast, PC patients mostly do not care about this disorder until adolescence, so admission rate is less then PE. We suggest that the real frequency of the chest wall deformities may be found only by widespread field studies. Moreover, we found more accompanying cardiac disorders in PC group, and this type of screening may allow early diagnosis of some cardiac diseases.

Keywords: Chest wall deformity; pectus carinatum; pectus excavatum

Corresponding Author[a]: Şevki Mustafa Demiröz, MD. Department of Thoracic Surgery, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey
E-mail: demirozsm@gmail.com

Received 23.10.2016 accepted 27.11.2016

Introduction

Chest wall deformities are a group of diseases changing the symmetric structure of the chest wall [1]. Most of these deformities do neither threat life nor lead a functional disorder. The classification by Willital offers 11 sub-branches for chest wall deformities which consists of pectus excavatum (PE) (4 subtypes), pectus carinatum (PC) (4 subtypes), mixed type, chest wall aplasia/hypoplasia and sternal cleft [2] (Table 1). The most frequent type of chest wall deformities is PE which consists of nearly 90% of the whole group [3].

In our study a definite population of otherwise healthy school children is screened to define the prevalence of chest wall deformities, to compare these data with the literatüre and children with deformity were invited to our hospital to make additional tests and the definitive treatment.

Table 1. Willital classification for congenital chest wall deformities

Type	(%)	Description
Type 1	(45)	Symmetrical funnel chest otherwise normal thorax
Type 2	(15)	Asymmetrical funnel chest otherwise normal thorax
Type 3	(22)	Symmetrical funnel chest and platythorax
Type 4	(8)	Asymmetrical funnel chest and platythorax
Type 5	(2)	Symmetrical pigeon chest, otherwise normal thorax
Type 6	(1)	Asymmetrical pigeon chest otherwise normal thorax
Type 7	(2)	Symmetrical pigeon chest and platythorax
Type 8	(1)	Asymmetrical pigeon chest and platythorax
Type 9	(2)	Combination of funnel chest and pigeon chest
Type 10	(1)	Aplasia of the ribs
Type 11	(1)	Manubrium - sternal cleft

Materials and Methods

An ethics committee approval and required permission was obtained from the Turkish Ministry of Health Kahramanmaraş Health Administration. A screening team consisting of a thoracic surgeon, a pulmonologist and a pediatrician was established. Screening was performed by visiting children in predefined elementary schools. The children identified with a chest wall deformity, were invited to hospital with his/her family. This group had undergone additional tests to clarify if a surgical treatment was indicated. Results were classified and compared with recent studies.

Results

A total of 25117 students between 6-11 years (mean 8.54) were included. The 56.9% of children were girls and 43.1% were boys. A total of 255 (1,01%) individuals with a chest wall deformity were invited to hospital for further evaluation. These were classified according to the type of deformity and additional tests were performed. Results were compared with recent studies.

231 of 255 cases (90.58%) had PC, 14 had PE (5.49%) and 10 had mixed PE+PC deformity (Table 2).

Table 2. Summary of the results

Age	6-11 (mean 8.54)		M/F ratio	
Gender	n	(%)	PC	3.2
Male	10.869	43.1	PE	1.0
Female	14.248	56.9	PE+PC	1.5
Deformity	n	(%)	Frequency(%)	
PC	231	90.58	0.92	
PE	14	5.49	0.055	
PE + PC	10	3.93	0.039	
Total	255	100	1.01	

128 cases had an abnormal electrocardiogram (ECG) record. The most frequent ECG abnormality seen in 49 cases (19% of cases with deformity) was a negative T wave on V1 derivation and a biphasic T wave configuration on V1-V2 derivations. 8 patients (3.13%) had concomitant scoliosis. 6 patients (2.35%) had different degrees of cardiomegaly (Table 3).

Table 3. Distribution of accompanying pathologies

Deformity		Scoliosis	Cardiomegaly	ECG changes
	n	n (%)	n (%)	n (%)
PC	231	7 (3.03)	6 (2.59)	118 (51.08)
PE	14	1 (7.14)	-	6 (42.8)
PE+PC	10	-	-	4 (40)
Total	255	8 (3.13)	6 (2.35)	128 (50.19)

Discussion

A morphologic classification which is defined as "Willital Classification", is generally used for classifying chest wall deformities [2]. When abnormalities such as Pentalogy of Cantrell, sternal cleft and Poland's Syndrome which make only 3.4% are excluded, chest wall deformity mostly refers to pectus deformities and especially pectus excavatum (PE) with a frequency of more than 90% in the literatüre [4].

Pectus Excavatum

Pektus excavatum, or "Funnel chest", is the most frequent type of chest wall deformity. It is the depression of the anterior chest wall in a symmetric or asymmetric manner due to abnormal growth of sternum and / or costal cartilage. In a report by Robiscek and colleagues, it is stated that this deformity is seen in 0.32% of all births by 9 times more in males [5]. Matos et al. stated that while the percentage reported was changing between different authors, its incidence was 0.1% by a male/female ratio of 3.3 [6]. Nuss et al. reported male / female ratio as 4 in their series of 148 cases [7]. Yüksel et al. reported that PE was seen 1 per 300-400 live births [8]. Brochhausen et al. reported an incidence of 0.1-0.8% and a male/female ratio between 2 and 9 [4].

In this study, we have found that PE consists only in 5,49% of all chest wall deformities, and its ratio in general population was 0.05%. Male / female ratio was found to be equal. When compared to previous two other studies made in Turkey, our data was similar with the report by Yücesan et al. who had found PC incidence higher [9]. But the other report by Esme et al. a states a higher PE incidence [10]. Groetsky et al. also reported a higher PC incidence than PE in Argentina [11].

Robiscek et al. stated that PE was a recessively transmitting disease, but Jarowski et al. reported that although 40% of the cases had a family history, it was not possible to introduce a strict relation to genetics [5,12]. Wu et al. reported that the disease was a recessive genetic disease and 40% of the cases had a family history of chest wall deformity, besides they defined a mutation on GAL3ST4 gene [13]. In the etiopathogenesis of PE, intrauterine compression, rickets, pulmonary restriction and insufficiency in osteogenesis or chondrogenesis were the considered theories [14]. In our study, a positive family history was present in only 2 PE cases (14.2%).

According to Robiscek et al. a majority of patients suffered from decreased effort capacity, decreased mobility, chest pain, palpitation and recurrent pulmonary infections [5]. Matos et al. reported that majority of the cases were asymptomatic until adolescence but suffered from decrease in effort capacity and dyspnea [6]. Nuss et al. stated that exercise intolerance, recurrent pulmonary infections and symptoms of asthma were present in these patients [7]. Johnson et al. defined the most frequent symptoms in PE as decreased capacity of exercise and chest pain [15].

On the other hand Oezcan et al. evaluated 18 patients who had a pectus index greater than 3 with echocardiography and cardiac magnetic resonance imaging, and found the most frequent concomitant cardiac pathologies as pericardial effusion, a left-sided cardiac shift and tricuspid valve prolapse [6]. In our study the most frequent symptoms in PE were cosmetic discomfort in 5 (35.7%), chest pain in 2 (14.8%) and dyspnea in 2 (14.8%) patients.

Nuss et al. found 5 Marfan Syndrome and 2 Ehlers Danlos Syndrome in a series of 127 PE patients [7]. Also Robiscek et al. reported that scoliosis, mitral valve disease and Marfan Syndrome might accompany PE [5]. Töpper et al. showed an increase in ejection fraction of the right ventricle following the surgical correction of PE in a prospective study [17]. In our study one patient had an accompanying scoliosis and 3 of the patients had negative T wave on anterior chest derivations on ECG.

In physical examination, the typical pectus posture is seen, which is, thin and tall children with a symmetric or asymmetric sternal depression, depressed shoulders, an increase in thoracic kyphosis and a relative bump on the abdomen. Accompanying pathologies such as scoliosis, asymmetric scapula, shift of cardiac apex beat, cardiac murmur, tachycardia, and arrhythmia may be present [4].

The degree of depression, location of the mediastinal organs and accompanying scoliosis are evaluated by chest x-ray and computed tomography. The pectus index defined by Haller et al. in 1987 is the ratio of transverse to antero-posterior dimension of chest wall on the most distinct depression. It is used for determining the degree of the deformity and surgical indication in PE. According to this index, a value lower than 2.56 is defined as normal, while higher than 3.25 suggests surgical correction. This index has replaced the old index defined by Welch in 1980, which suggested estimating the distance between vertebra and sternum in lateral chest x-ray [18] (Figure 1).

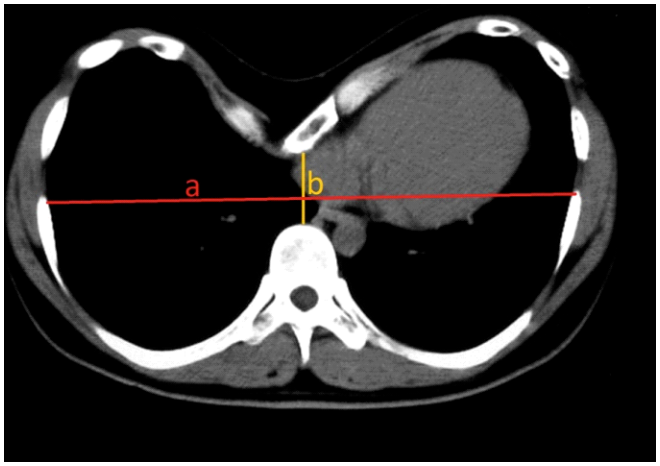


Figure 1. A computed tomography showing the calculation of Haller index (a/b)

The management of PE is on a wide range from observation by follow up to surgical treatment or non-surgical treatments like silicone or vacuum therapy. The minor deformity which doesn't lead to physiologic or psychological problems may be observed and followed up until the adolescence. Jarozewski and colleagues have defined surgical indications in PE [12] (Table 4).

Table 4. Criteria for surgical referral
Symptomatic
Progression of the deformity
Paradoxical movement of the chest wall with deep inspiration
Computed tomography with severity index >3.0
Cardiac compression or displacement
Pulmonary compression
Abnormal pulmonary function tests showing significant restrictive disease
Mitral valve prolapse
Any cardiac pathology secondary to compression of the heart
Significant body image disturbance
History of failed previous repair
Abnormal cardiopulmonary testing

Zang et al. defined surgical indications for pectus correction in a series of 639 cases as, Haller index bigger then 3.25, restrictive or obstructive pattern in respiratory function tests, valve prolapse on ECG or echocardiography, presence of a progressive and symptomatic deformity, physicosocial problems due to abnormal body structure, recurrence in patients underwent previous surgery [19]. Historically the first successful surgery for PE was reported by Meyer in 1911 followed by reports defining different techniques until the development of minimally invasive techniques we use today.

The milestone in PE surgery is the report by Ravitch describing his new technique and giving the results of 8 cases. In subject report Ravitch had classified surgical indications in main three topics; cosmetic, orthopedic and physiologic. His technique was consisting of a vertical incision on sternum, subperichondrial total resection of deformed cartilages, the resection of intercostal bands, resection of the xiphoid process, sternal osteotomy and a substernal transverse Kirschner wire placement between the remaining costae [20]. This technique was applied with some modifications in the following years. The sternal turnover technique defined by Wada in 1960 was used until 1970 on 271 cases but it was then left due to high complication rate [21].

In 1978, Robiscek have modified the technique of Ravitch by using a marlex mesh. In this technique after the mobilization of the sternum a transverse osteotomy is made, parasternal costal cartilages were resected and then a marlex mesh is laid behind the sternum between the ends of the resected costa for chest wall stabilization [22]. Also Robiscek et al. determined the surgical indications as: i) This surgery may be performed in any age, ii) Morbidity must be kept in minimal and must not be prolonged, iii) No mortality is allowed, iv) The anatomic result must be perfect [5].

Gurkok et al. defined a new technique for PE correction which an absorbable plaque is placed with polymer screws on the point of osteotomy but the main disadvantage of this technique is high costs [23,24].

The minimally invasive technique in PE correction was defined by Donald Nuss in 1998 on 50 patients. This technique is called by his name as "Nuss Procedure" [7]. In this procedure, while the cosmetic results, pain control and the days of hospital stay is more favorable then open surgical techniques, some serious complications such as pneumothorax, pleural effusion, cardiac injury and dislocation of the bar may be seen [25,26]. In our study, surgical PE correction with Nuss procedure was offered to 9 patients who had cosmetic problems and physical symptoms.

Pectus Carinatum

According to the majority of the literatüre, it is a more rare deformity when compared with PE with a prevalence of 0.06-0.09% [27]. But, Goretsky et al. reported that it was seen more than PE in Argentina [11]. It is more frequent in males [27]. Robiscek and colleagues

reported male / female ratio as 4 in 2010 [28]. Fonkalsrud reported a 6 fold male incidence [29]. The etiology is not clear like PE, but the most common view is the abnormal development of costal cartilages [30]. In our study, in contrast with the literature, the vast majority of the deformities were PC (90.5%). We think that the main cause of this difference is because the notification of PE is easier by the children themselves or by their families and it is thought to be a severe condition, so the hospital admissions are much more than PC. As a result, the hospital incidence of PE is greater than PC.

PC is also classified as symmetric or asymmetric due to the place of the sternal protrusion. As PE, Marfan syndrome, homocystinuria, Prune belly syndrome, Morquio syndrome and mitral valve prolapse may accompany PC, too [28]. Coelho et al. reported 16.4% accompanying asthma and chronic bronchitis and in almost whole patients kyphosis in different degrees [27]. Robiscek et al. reported that one third of the patients had a family history while Park et al. reported that 25% of patients said that a chest wall deformity was present in the family [28, 30]. In our study the incidence of PC was 0.91% of all the study population. Male / female ratio was 3.2 which was similar to the literature. But when family history is questioned, a positive history ratio of 3.03% was found and this was really low when compared to the literature. We think the cause of this low ratio may be due to mild deformities which are not defined as an abnormality by the people.

Coelho et al. reported that palpitation and dyspnea triggered by effort were the symptoms of PC. Also these patients avoided activities such swimming or other sports which might expose their deformity [27]. Fonkalsrud reported that symptoms in PC rarely came out in early childhood, mostly they began in adolescence and the most frequent ones were dyspnea, exercise intolerance and exersize associated wheezing. But the most disturbing state is the cosmetic one for an adolescent [29]. In our study the most frequent symptoms were found as dyspnea, palpitation and exercise intolerance, too. In 7 patient with PK (3.03%) accompanying scoliosis and in 6 patients (2.59%) different degrees of cardiomegaly was found.

There is limited experience with using supportive materials and chest compressors for the treatment of PC. For surgical treatment, Robiscek and Ravitch defined costochondral resection and sternotomy technique. In this technique, whether a unilateral deformity is present, it is important to make bilateral cartilage resections for preventing recurrence [11]. In the report by Robiscek in 2011, the below listed points were emphasized in modern PC surgery. The technique must be easy and feasible for fast application, must not require permanent foreign material in the body, must not lead to severe complications, must have a perfect cosmetic and functional result, must not require long and frequent postoperative control and must not require re-intervention.

The minimally invasive technique was defined by Abramson in 2008. In his report 40 cases were evaluated in terms of effectiveness. In this technique, the bar was introduced subcutaneously through bilateral incisions on the chest wall.

Minimally invasive technique in PC is used in the chondrogladiolar subtype. According to this report, the advantages of this minimally invasive technique are listed as [31], lack of incisions in the anterior thoracic region, avoiding scars and the presence of keloid formation, short surgery time and minimal blood loss, short hospitalization and recovery time, improvements in the thoracic contour because of correction of the protrusion and widening of base of both hemithorax without losing elasticity in the thoracic cage, very good long term results without recurrences.

The metal bar designed by Yuksel et al. was used in 18 cases with the technique defined by Abramson and they had very satisfactory results (32). In our study, considering the degree of the deformity and the present symptoms 47 patients (20.3%) were offered a surgical correction.

In conclusion, we think that for calculating the real incidence of chest wall deformities in the population, widespread screening studies must be designed at schools, military camps and colleges instead of counting hospital admissions. In our study, in contrast with the literature, 90% of the deformities were found to be PC. The “family history” definition is a subjective data and families also must be included in screening programs. Moreover, we found more accompanying cardiac disorder in PC group, and this type of screening may allow early diagnosis of some cardiac diseases.

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.

References

1. Anger J, Francisco R, Alcalde V, de Campos JR. The use of soft silicone solid implant molded intraoperative for pectus excavatum surgical repair. Einstein 2014; 12: 186-90.
2. Saxena AK. Pectus excavatum, pectus carinatum and other forms of thoracic deformities. J Indian Assoc Pediatr Surg 2005; 10: 147-57.
3. Kuru P, Cakiroglu A, Er A, Ozbakir H, Cinel AE, Cangut B, et al. Pectus excavatum and pectus carinatum: Associated conditions, family history, and postoperative patient satisfaction. Korean J Thorac Cardiovasc Surg 2016; 49: 29-34.
4. Brochhausena C, Turialb S, Müllera KF, Schmitta VH, Coerdta W, Wihlmc JM, et al. Pectus excavatum: history, hypotheses and treatment options. Interact Cardiovasc Thorac Surg 2012; 14: 801–6.
5. Robicsek F, Watts LT, Fokin AA. Surgical Repair of pectus excavatum and carinatum. Semin Thorac Cardiovasc Surg 2009; 21: 64-75.
6. de Matos AC, Bernardo JE, Fernandes LE, Antunes MJ. Surgery of chest wall deformities. Eur J Cardiothorac Surg 1997; 12: 345-50.
7. Nuss D, Kelly RE, Crotioru DP, Katz ME. A 10 year review of a minimally invasive technique for the correction of pectus excavatum. J Pediatr Surg, 1998; 33: 545-52.
8. Yuksel M, Bostanci K, Evman S. Minimally invasive repair after inefficient open surgery for pectus excavatum. Eur J Cardiothorac Surg 2011; 40: 625-9.
9. Yucesan S, Dındar H, Olcay I, Okur H, Kilicaslan S, Ergoren Y, et al. Prevalence of congenital abnormalities in Turkish school children Eur J Epidemiol 1993; 9: 373-80.
10. Esme H, Bukulmez A, Dogru O, Solak O. Prevalence of chest wall deformities in primary school children of Afyon city. Turkish J Thorac Cardiovasc Surg 2006; 14: 34-7.
11. Goretsky MJ, Kelly RE, Jr, Croitoru D, Nuss D. Chest wall anomalies: pectus excavatum and pectus carinatum. Adolesc Med 2004; 15: 455-71.
12. Jaroszewski D, Notrica D, McMahon L, Steidley E, Deschamps C. Current management of pectus excavatum: A review and update of therapy and treatment recommendations. JABFM 2010; 23: 230-39.
13. Wu S, Sun X, Zhu W, Huang Y, Mou L, Liu M, et al. Evidence for GAL3ST4 mutation as the Potential cause of pectus excavatum Cell Res 2012; 22: 1712-5.
14. Tocchioni F,Ghionzoli M, MessineoA, Romagnoli P. Pectus excavatum and heritable disorders of the connective tissue. Pediatric Reports 2013; 5: 58-63.
15. Johnson WR, Fedor D, Singhal S. Systematic review of surgical treatment techniques for adult and pediatric patients with pectus excavatum. J Cardiothorac Surg 2014, 9: 25.
16. Oezcan S, Attenhofer Jost CH, Pfyffer M, Kellenberger C, Jenni R, Binggeli C, et al. Pectus excavatum: echocardiography and cardiac MRI reveal frequent pericardial effusion and right-sided heart anomalies. Eur Heart J Cardiovasc Imaging 2012; 13: 673-9.
17. Töpper A, Polleichtner S, Zagrosek A, Prothmann M, Traber J, Schwenke C, et al. Impact of surgical correction of pectus excavatum on cardiac function: insights on the right ventricle. A cardiovascular magnetic resonance study. Interact CardioVasc Thorac Surg 2016; 22: 38-46.
18. Haller JA, Kramer SS, Lietman SA. Use of CT scans in selection of patients for pectus excavatum surgery: A preliminary report. J Pediatr Surg 1987; 22: 904-6.
19. Zhang DK, Tang JM, Ben XM, Xie L, Zhou HY, Ye X, et al. Surgical correction of 639 pectus excavatum cases via the Nuss Procedure. J Thorac Dis 2015; 7: 1595-605.

20. Ravitch MM. The operative treatment of pectus excavatum. Ann Surg 1949; 129: 429-44.

21. Wada J, Ikeda K , Ishida T, Hasegawa T. Results of 271 funnel chest operations. Ann Thorac Surg 1970; 10: 526-32.

22. Robicsek F. Marlex mesh support for the correction of very severe and recurrent pectus excavatum. Ann Thorac Surg 1978; 26: 80-3.

23. Gurkok S, Genc O, Dakak M, Balkanli K. The use of absorbable material in correction of pectus deformities. Eur J Cardiothorac Surg 2001; 19:711-2.

24. Ozpolat B, Soyal T, Gokaslan G, Tophanelioglu T, Sarigül A,Yücel E. Surgical correction of pectus excavatum and carinatum deformities: evaluation of 30 cases. Turkish J Thorac Cardiovasc Surg 2005; 13: 270-3.

25. Cheng YL, Lin CT, Wang HB, Chang H. Pleural Effusion Complicating after Nuss Procedure for pectus excavatum. Ann Thorac Cardiovasc Surg 2014; 20: 6-11.

26. Sa YJ, Lee J, Jeong JY, Choi M, Park SS, Sim SB, et al. A clinical decision-making model for repeat surgical treatment of pectus Bar displacement: distance measurement after nuss procedure. J Cardiothorac Surg 2016; 11: 16.

27. Coelho S, Guimaraes S. Pectus carinatum. J Bras Pneumol 2007; 33: 463-74.

28. Robicsek F, Watts LT. Pectus carinatum. Thorac Surg Clin 2010; 20: 563-74.

29. Fonkalsrud EW. Pectus Carinatum: The undertreated chest malformation. Asian J Surg 2003; 26: 189-92.

30. Parka CH, Kima TH, Haamb SJ, Lee S. Does overgrowth of costal cartilage cause pectus carinatum? A three-dimensional computed tomography evaluation of rib length and costal cartilage length in patients with asymmetric pectus carinatum. Interact Cardiovasc Thorac Surg 2013; 17: 757-63.

31. Abramson H, D'Agostino J, Wuscovi S. A 5-year experience with a minimally invasive technique for pectus carinatum repair. J Pediatr Surg 2009; 44:118-24.

32. Yuksel M, Bostanci K, Evman S. Minimally invasive repair of pectus carinatum using a newly designed bar and stabilizer: a single-institution experience. Eur J Cardiothorac Surg 2011; 40: 339-42.

Current Thoracic Surgery

To cite this article: Öz N, Kargı AB, Kargı A, Yıldız A, Yılmaz S. Multimodality treatment of primary mediastinal germ cell tumor with growing teratoma syndrome: a case report. Curr Thorac Surg 2016; 1(1):28-31.

Case Report

Multimodality treatment of primary mediastinal germ cell tumor with growing teratoma syndrome: a case report

Necdet Öz[1a], Ahmet Bülent Kargı[2], Ayşegül Kargı[3], Akın Yıldız[4], Saim Yılmaz[5]

[1]Department of Thoracic Surgery, Medstar Antalya Hospital, Antalya, Turkey
[2]Department of Thoracic Surgery, Medicalpark Antalya Hospital, Antalya, Turkey
[3]Department of Medical Oncology, Medstar Antalya Hospital, Antalya, Turkey
[4]Department of Nuclear Medicine, Medstar Antalya Hospital, Antalya, Turkey
[5]Department of Interventional, Medstar Antalya Hospital, Radiology Antalya, Turkey

ABSTRACT

Germ cell tumors arise from errors occurring during the migration of embryonic stem cells to the gonads. They constitute 10-15% of malignant mediastinal tumors. Thirty-nine years old male patient was admitted with shortness of breath and gynecomastia. Positron emission tomography / Computed tomography (PET/CT) showed hypermetabolic mediastinal mass in the anterior mediastinum. Serum tumor markers were elevated. Mixed germ cell tumor was diagnosed via transthoracic tru-cut biopsy. After three cycles of systemic cisplatin, etoposide and bleomycin treatment, PET/CT showed a decreased metabolic activity but an increase in the size of mass. "Growing teratoma syndrome" was diagnosed. The excision of the mass was performed via a median sternotomy. Then autologous stem cell transplantation was performed. Patients was presented as a successful example of a multimodality treatment of a primary mediastinal germ cell tumor with GTS.

Keywords: Germ cell tumor; mediastinal mass; growing teratoma syndrome; surgery

Corresponding Author[a]: Necdet Öz, MD. Department of Thoracic Surgery, Medstar Antalya Hospital, Antalya, Turkey.
E-mail: drnecdetoz@gmail.com

Received 28.03.2016 accepted 11.07.2016

Introduction

Germ cell tumors are originated from the remnants of gonadal pluripotent cells during the embryological migration. Extragonadal germ cell tumors involve 75% of the mediastinal masses. More than 80% of mediastinal germ cell tumors are benign [1,2]. The "Growing teratoma syndrome" (GTS) is a rare condition which is seen in nonseminomatous germ cell tumors (NSGCT). Sometimes, the tumor growing is observed during or after a chemotherapy and named as GTS. It was first described in 1982 by Logothetis et al. and occurs in %2-7 of all NSGCT [3]. They defined three criteria which are, normalization of the serum tumor markers, an increase in the diameter of the mass and presence of mature teratoma in the resected specimen [3].

In this case report we report the PET/CT findings a patient with GTS, and his successful treatment after a multidisciplinary planning.

Case Report

A thirty nine-years old male patient presented with bilateral gynecomastia and dyspnea for two months. On physical examination, decreased breath sounds on the left hemithorax, bilateral gynecomastia were observed. Genital examination was normal. Chest x-ray and thoracic computed tomography (CT) showed 17x8 cm mass covering the whole anterior mediastinum and pushing the heart to the right. The mass included micro calcifications and invaded vascular structures and pericardium. Positron emission tomography/Computed tomography (PET/CT) reported high metabolic activity in the heterogeneous mass lesion (SUVmax: 17.8) (Figure 1).

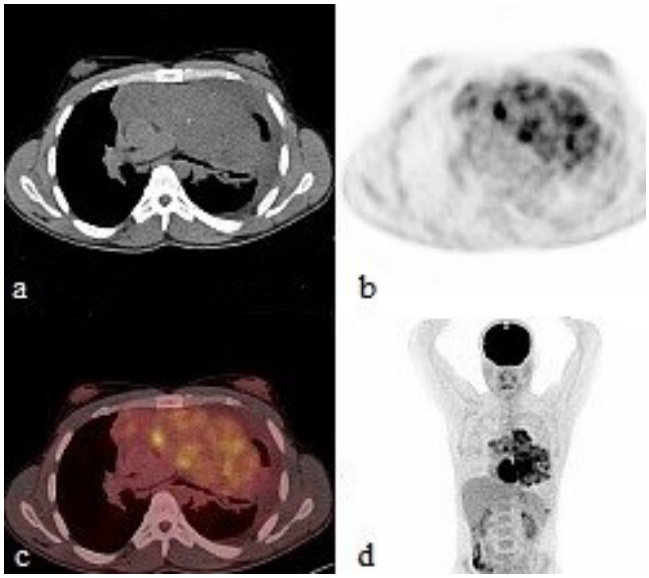


Figure 1. PET/CT demonstrating hypermetabolic anterior mediastinal mass

There was also a hypermetabolic nodule in the left pleural space and a non-metabolic left pleural effusion. Testicular ultrasound was normal. Serum AFP level was 3000 IU/dl (0-9 ng/mL), ß-hCG level was 555 IU/dl (0-2.67 mIU/mL). Pathologic diagnose was “mixed germ cell tumor” by CT guided tru-cut biopsy. The TNM classification was stage II. Three cycles of chemotherapy involving cisplatin, etoposide and bleomycin (BEP) therapy were applied. After the chemotherapy, patient was re-evaluated for treatment. PET/CT reported decreased metabolic activity (SUVmax: 5.5) but the tumor size increased to 21x9 cm (Figure 2).

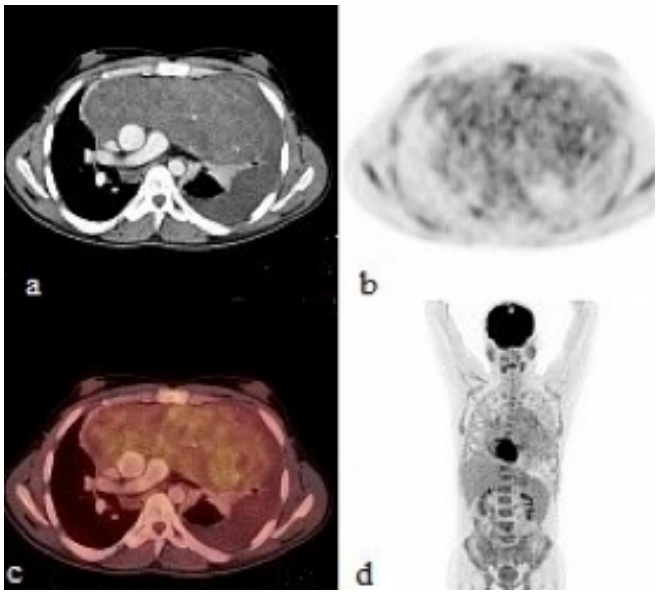


Figure 2. PET/CT demonstrating that the diameters of the anterior mediastinal mass increased but metabolic activity decreased.

The AFP level was 14 ng/mL. The diagnosis of the overall examination was "Growing teratoma syndrome". Mediastinal mass was excised totally by median sternotomy. Macroscopic tumor size was 23 x 17 cm (Figure 3a). Pathological examination was reported as immature teratoma. Immature teratoma component originated from primitive mesoderm was 1-2%. Tumor included a necrotic area of %30-40 (Figure 3b).

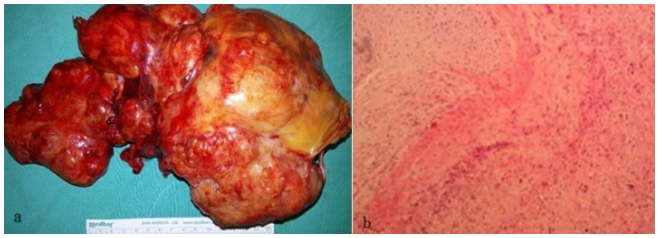


Figure 3. The pathologic findings of the resected tumor. a-The macroscopic view of mass, and b-histopathological view of immature teratoma (hematoxylin-eosin x 4).

Post-operative AFP level decreased to 9.3 ng/mL and ß-hCG remained within normal limits. After high-dose chemotherapy contains isophosphomide, carboplatin and etoposide, autologous stem cell transplantation (ASCT) was performed. The patient has been in the remission for two years.

Discussion

Although mediastinal tumors are often asymptomatic, some symptoms such as chest pain, dyspnea, cough, and fever may occur. Symptoms are related the compression to vascular structures, airways and esophagus [1,2]. Teratomas can secrete hormones leading paraneoplastic syndromes as seen in this case.

Determination of a mediastinal mass with radiological methods and elevation of serum AFP and ß-hCG may be enough for the diagnosis of NSGCT. Pathological examination provides an accurate diagnoses by revealing if an immature component exists. A tomography guided fine-needle biopsy or core biopsy can give a minimal invasive and successful diagnostic result. If this procedure is inadequate, it may be performed via a cervical mediastinoscopy, anterior mediastinotomy or thoracoscopy [4].

Mediastinal germ cell tumors frequently uptake FDG and PET/CT is used for staging and monitoring the metabolic response to chemotherapy, and also residue or recurrence of the tumor [5,6]. In this case the PET/CT was an essential tool for the diagnosis of GTS, showing a high metabolic activity and heterogeneity. After induction chemotherapy, the second PET/CT showed a decrease in the metabolic activity even though the diameters of the mass increased. The morphological and metabolic response mismatch findings supported the mixed nature of the mass [6].

The standard treatment of germ cell tumor must contain platinum-based regimen. The most common combination regimens are BEP (bleomycin etoposide, and cisplatin) and VIP (Isofosfamide, Etoposide, and Cisplatin) [7-9]. After three or four cycles of chemotherapy in case of full response, the patient must be followed without drugs. After chemotherapy, although tumor markers return to normal range, the mass grows up. In the presence of residual tumor or GTS surgical resection are proposed by most authors. [10-12] Sometimes the patient with GTS may refer in a bad condition and urgent operation may be necessary [10].

Sarkaria et al. [7] reported good prognostic factors in a series of 43% mixing type of totally 56 NSGCT patients as, R0 surgical resection after standard BEP chemotherapy, postoperative pathology demonstrates necrosis instead of teratoma, descending tumor marker levels after chemotherapy and prior stage I-II.

Walsh et al. [13] reported that an additional radical surgical resection to the initial standard or intensive chemotherapy after recurrence, increased the survey. Rodney et al. [14] suggested 3 poor prognostic factors as, serum ß-hCG level greater than 1,000 mIU/mL at diagnosis, presence of extra mediastinal disease and any mixed and single histologic diagnosis other than ectodermal sinus tumors. Accordingly in our case final pathological examination was reported as immature teratoma which is a prognostic factor.

Autologous stem cell transplantation following high-dose chemotherapy is defined as a treatment option for selected patients [8,15,16]. Bone marrow is affected by chemotherapy and regains the functions with ASCT. Bokemeyer et al [15] reported that according to "International Germ Cell Tumor Group Consensus Classification" the patients in the middle and poor prognosis groups benefit from high-dose chemotherapy and ASCT as a first treatment, instead of the standard treatment and the survey increases by %15. In this case, surgical excision followed by VIP chemotherapy and pathologic examination showed immature teratoma including 30%-40% necrosis. Although tumor markers and FDG uptake decreased the mass included more than 1% viable tumor cells so the high risk patient went to high-dose chemotherapy, and autologous ASCT.

In conclusion, we present this case as PET/CT findings of GTS was interesting, besides the patient was treated a successful instance of planning and treatment with medical oncology, thoracic surgery, hematology, and nuclear medicine clinics, i.e. multidisciplinary.

Declaration of conflicting interests

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

Funding

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

References

1. Hainsworth JD, Greco FA. Nonseminomatous malignant germ cell tumors of the mediastinum. In: Shields TW, Locicero J, Reed CE, Feins RH, editors. General Thoracic Surgery. Philadelphia: Wolters Kluwer Lippincott Williams&Wilkins; 2009. p. 2403-9.
2. Kang CH, Kim YT, Jheon SH, Sang S, Sung S, Kim JH. Surgical treatment of malignant mediastinal nonseminomatous germ cell tumor. Ann Thorac Surg 2008; 85:379-84.
3. Logothetis CJ, Samuels ML, Trindade A, Johnson DE. The growing teratoma syndrome. Cancer 1982; 50:1629-35.
4. Shinagare AB, Jagannathan JP, Ramaiya NH, Hall MN, Van den Abbeele AD. Adult extra gonadal germ cell tumors. Am J Roentgen 2010; 195: 274-80.
5. Rankin S. 18F-2-Fluoro-2-deoxy-d-glucose PET/CT in mediastinal masses. Cancer Imaging. 2010; 10(1A): S156-S160.
6. Agatsuma T, Koizumi T, Kubo K, Saito G, Kondo R, Yoshida K, et al. Mediastinal growing teratoma syndrome successfully treated by multiple modality therapies. Intern Med 2011; 50: 607-10.
7. Sarkaria IS, Bains MS, Sood S, Sima CS, Reuter VE, Flores RM, et al. Resection of primary mediastinal non-seminamatous germ cell tumors: A 28-years' experience at Memorial Sloan-Kettering Cancer Center. J Thorac Oncol 2011; 6: 1236-41.
8. Date H, Kiura K, Ueoka H, Tabata M, Hotta K, Katayama H, et al. Induction chemotherapy, surgical resection, and high-dose chemotherapy for mediastinal nonseminamatous germ-cell tumor. J Thorac Cardiovasc Surg 2003; 130: 1205-6.
9. Iyoda A, Hiroshima K, Yusa T, Toyozaki T, Fujisawa T, Ohwada H. The primary mediastinal growing teratoma syndrome. Anticancer Res 2000: 20(5C): 3723-6.
10. Kesler KA, Patel JB, Kruter LE, Birdas TJ, Rieger KM, Okeroke IC, et al. The ''growing teratoma syndrome'' in primary mediastinal nonseminomatous germ cell tumors: Criteria based on current Practice. J Thorac Cardiovasc Surg 2012; 144: 438-43.
11. Li-Tzong Chen, Cheng-Lung Chen, and Wei-Shou Hwang. The growing teratoma syndrome. A case of primary mediastinal nonseminomatous germ cell tumor treated with chemotherapy and Radiotherapy. Chest 1990; 98: 231-3.
12. Tongaonkar HB, Desmane VH, Dalal AV, Kulkarni JN, Kamat MR. Growing teratoma syndrome. J Surg Oncol 1994; 55: 56-60.
13. Walsh GL, Taylor GD, Nesbitt JC, Amato RJ. Intensive chemotherapy and radical resections for primary nonseminomatous mediastinal germ cell tumors. Ann Thorac Surg 2000; 69: 337-44.
14. Rodney AJ, Tannir NM, Siefker-Radtke AO, Liu P, Walsh GL, Millikan RE, et al. Survival outcomes for men with mediastinal germ-cell tumors: The university of Texas M.D Anderson Cancer Center experience. Urol Oncol 2012; 30: 879-85.
15. Bokemeyer C, Schleucher N, Metzner B, Thomas M,Rick O,Schmoll H-J, et al. First-line sequential high-dose VIP chemotherapy with autologous transplantation for patient with primary mediastinal nonseminamatous germ cell tumours a prospective trial. British J Cancer 2003; 89: 29-35.
16. Kuwano H, Tsuchiya T, Murayama T, Sano A, Nagayama K, Yoshida Y, et al. Outcomes of combined modality therapy for patients with stage III or IV mediastinal malignant germ cell tumors. Surg Today 2014; 44: 499-504.

Current Thoracic Surgery

To cite this article: Kaya S, Pur Yiğit L, Erelel M, Toker A. Expectoration of a tumor tissue: metastatic endobronchial leiomyosarcoma treated with endoscopy. Curr Thorac Surg 2016;1(1):32-34.

Case Report

Expectoration of a tumor tissue: metastatic endobronchial leiomyosarcoma treated with endoscopy

Serkan Kaya[1a], Leyla Pur Yigit[2], Mustafa Erelel[3], Alper Toker[4]

[1]Department of Thoracic Surgery, School of Medicine, Namık Kemal University, Tekirdağ, Turkey
[2]Department of Allergy-Immunology, School of Medicine, Koç University Hospital, İstanbul, Turkey
[3]Department of Chest Disease, İstanbul School of Medicine, İstanbul University, İstanbul, Turkey
[4]Department of Thoracic Surgery, İstanbul School of Medicine, İstanbul University, İstanbul, Turkey

ABSTRACT

A 57-year-old male patient was admitted to our department with symptoms of dyspnea and hemoptysis, followed by a spontaneous expectoration of a small piece of solid tissue. He had two operations 13 and 3 years ago for perineal leiomyosarcoma and was on intermittent chemotherapy regimen until last year. Computerized chest tomography revealed an endotracheal mass with multiple metastatic nodular lesions at both lung fields. The pathologic examination of the expectorated tissue was found to be consistent with the metastasis of leiomyosarcoma. Solid polypoid endotracheal lesion adherent to the anterolateral wall and obstructing 70% of trachea was excised with the rigid bronchoscopy and argon laser.

Keywords: Endotracheal; hemoptysis; dyspnea; leiomyosarcoma; bronchoscopy

Corresponding Author[a]: Serkan Kaya, MD. Department of Thoracic Surgery, School of Medicine, Namık Kemal University, Tekirdağ, Turkey.
E-mail: serkankaya@gmail.com

Received 29.03.2016 accepted 31.05.2016

Introduction

Leiomyosarcoma is an uncommon malignancy usually arising in the uterus or in the retroperitoneum which tends to metastasize to the lungs and liver. The trachea is rarely affected and tumor expectoration is an unusual presentation. In unusual circumstances bronchoscopy reveals an endobronchial polypoid lesion without involvement of the bronchial wall. These lesions could be excised by a rigid bronchoscopy. As they tend to be refractory to either chemotherapy or radiotherapy resection is needed immediately for palliation [1-5].

In this case report we present the successful treatment of a rare case of expectorated metastatic leimyosarcomas excised with rigid bronchoscopy and argon laser.

Case Report

A 57-year-old male patient was admitted to our department with symptoms of dyspnea and spontaneous expectoration of a small piece of solid tissue. He had two operations for perineal leimyosarcomas thirteen and three years ago and was on intermittent chemotherapy treatment with imatinib mesylate until last year, which was discontinued because of his intolerance. Two years ago parenchymal lung metastases were detected but they were steady without progression. His vital signs were normal. Physical examination revealed diminished breathing sounds in the both lower lung area and an incisional scar on his perineal region. He was unable to perform pulmonary function tests. His blood chemistry and hematologic studies were normal. Chest X-ray revealed multiple nodules in both lungs but computerized chest tomography revealed an endotracheal mass with multiple metastatic nodular lesions at both lungs (Figure 1). These findings were confirmed with a virtual bronchoscopy. The pathologic examination of the expectorated tissue was found to be metastasis of leiomyosarcoma. The specimen's immunohistochemical stains for actin, vimentin, were positive but desmin, keratin, S100, and CD34 were negative.

Fiberoptic bronchoscopy under local anesthesia revealed a large, white, glistening endotracheal lesion arising from the left anterolateral wall and obstructing %70 percent of the trachea (Figure 2a). With general anesthesia, a rigid bronchoscopy was performed and the lesion was successfully excised and argon coagulation was applied for hemostasis (Figure 2b). The specimen showed the identical pathology with the previous expectorated tissue. The patient had no complications, has recovered from is symptoms and was discharged from our clinic the next day. Two weeks after treatment, trachea was confirmed to be normal.

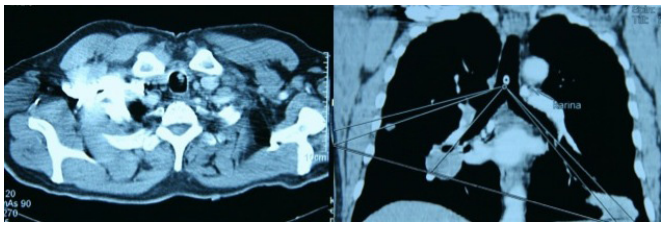


Figure 1. Computerized chest tomography of the patient.

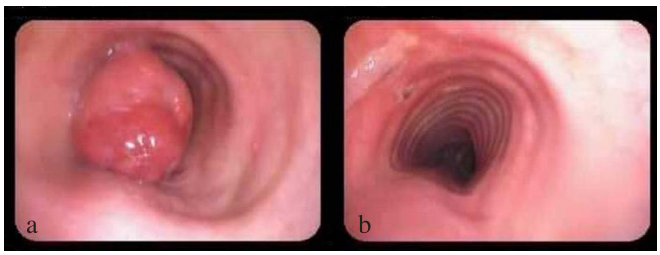


Figure 2. Fiberoptic bronchoscopy showing endotracheal tumor (a); after surgical resection and argon therapy (b).

Discussion

Primary neoplasms of the trachea are rare, in contrast to the larynx and the bronchial tree. Most common types of secondary tracheal tumors are infiltrating esophageal and thyroid cancers, or infiltrating lymph node metastasis [1]. Many variants of pulmonary metastasis could not be noticed with almost all kinds of malignant neoplasms. Extrapulmonary sources of endotracheal metastasis are very less common than pulmonary metastasis. Malignant neoplasms which could make metastasis to trachea are breast, colorectal, and renal neoplasms [2-3]. Metastatic leiomyosarcoma occasionally is seen with gross endobronchial extension without invasion of the bronchial wall. These patients have major airway obstruction and partial or total atelectasis of the lung [4]. Gynecologic leiomyosarcoma are uncommon malignancies. Although pulmonary metastases are frequent complications, endobronchial metastases are rare [5]. However, we have only two metastatic tracheal neoplasm patients (other one was colorectal metastasis to trachea) from 1997 on our department and working as a specific clinic as thoracic surgery. We performed a pubmed research with the key words of endotracheal, hemoptysis, dyspnea and leiomyosarcoma. We have found only 2 endobronchial - not endotracheal - metastasis of leiomyosarcoma [4,5]. We performed an endo-

tracheal treatment on this lesion and a tracheal approach for palliation using both fiberoptic and rigid bronchoscopy. We did not achieve a complete treatment since there were also pulmonary nodules but palliated and helped him breathing well and have a comfortable life. We believe that metastatic scan should be done carefully all over the body periodically; and should be taken care of immediately. Pulmonary metastases of leiomyosarcoma that he had, were uncountable number of nodules on both lung fields. The patient refused a chemotherapy treatment but nodule was excised and he is still doing well now for 12 months.

As a conclusion, the patients who had leiomyosarcoma neoplasms should be evaluated for endotracheal metastasis in case of acute airway obstruction. These lesions could be resected safely by endotracheal approach.

Declaration of conflicting interests

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

Funding

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

References

1. Krausser H, Skuballa A. Endotracheal neoplasm of a 16-year-old boy: Extremely rare primary localisation of a B-cell non-Hodgkin's lymphoma. Pneumologie 2003; 57: 208-11.
2. Watanabe S, Oda M, Ohta Y, Watanabe G. Endotracheal metastasis of rectal cancer. Eur J Cardiothorac Surg 2002; 21: 924.
3. Nguyen BD, Ram PC, Roarke MC. Endotracheal metastasis from squamous cell cancer of the head and neck: PET/CT imaging. Clin Nucl Med 2008; 33: 340-1.
4. Warren WH, Bleck P, Kittle CF, Faber LP. Surgical management of pulmonary metastatic leiomyosarcoma with gross endobronchial extension. Ann Thorac Surg 1990; 50: 739-42.
5. Richman M, Au J, Aoyama C, Kamangar N. Endobronchial metastases of gynecologic leiomyosarcoma: a case report and review of the literature. J Bronchology Interv Pulmonol 2007; 14: 131-3.

To cite this article. Alar T, Uysal A, Gedik İE. Catamenial pneumothorax: a case report of recurrent spontaneous pneumothorax. Curr Thorac Surg 2016;1(1): 35-37.

Case Report

Catamenial pneumothorax: a case report of recurrent spontaneous pneumothorax

Timuçin Alar[1a], Ahmet Uysal[2], İsmail Ertuğrul Gedik[1]

[1]Department of Thoracic Surgery, Faculty of Medicine, Çanakkale Onsekiz Mart University, Çanakkale, Turkey
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Çanakkale Onsekiz Mart University, Çanakkale, Turkey

ABSTRACT

Catamenial pneumothorax (CP) is a type of recurrent pneumothorax that occurs during menstrual periods in women. CP is a special type of pneumothorax related with the menstrual period and the treatment consists of both medical and surgical methods. First line of surgical treatment is exploration of thorax via VATS and revealing the pathophysiological factors of CP. Despite the surgical treatment techniques, a postoperative recurrence rate of CP is 30%. We present a recurrent pneumothorax case who had 5 pneumothorax episodes and diagnosed as CP. A left VATS apical wedge resection and pleurectomy was performed and oral contraceptive was administered. and she did not have a recurrent pneumothorax episode for last 2 years.

Key Words: Pneumothorax; catamenial pneumothorax; endometriosis

Corresponding Author[a]: Timuçin Alar, MD. Department of Thoracic Surgery, Faculty of Medicine, Çanakkale Onsekiz Mart University, Çanakkale, Turkey.
E-mail: timalar@yahoo.com

Received 21.06.2016 accepted 05.11.2016

Introduction

Catamenial pneumothorax (CP) which is derived from the Greek word catamenial meaning monthly. CP is a type of recurrent pneumothorax that occurs during menstrual periods in women of breeding age [1]. CP is a pneumothorax that starts within a time period of 24 hours before and 72 hours after the onset of a menstrual period [2]. The mean age of patients with CP is 35 years (range 15-54) [3]. It should be noted that thorax is the most common site of extra-pelvic endometriosis which is believed to be the primary etiological factor in CP.

We present a recurrent pneumothorax case who had 5 pneumothorax episodes and one of them is during the postoperative period, diagnosed as CP.

Case Report

A 28-year-old female patient presented to our hospital's emergency department with the chief complaint of left sided chest pain. Patient's history revealed that the pain started abruptly 4 hours before her admission and is aggravated by inspiration. Her history also revealed that she was in her menstrual period. She mentioned that she had similar left sided chest pain started during menstrual cycles twice last year. She admitted to other hospitals for these episodes and was treated with nasal oxygen inhalation therapy. This episode of pneumothorax was considered as the first episode because we couldn't obtain her past medical record. Physical examination revealed diminished left apical lung auscultation sounds. Left sided spontaneous pneumothorax was found in posterior-anterior (PA) chest x-ray (Figure 1).

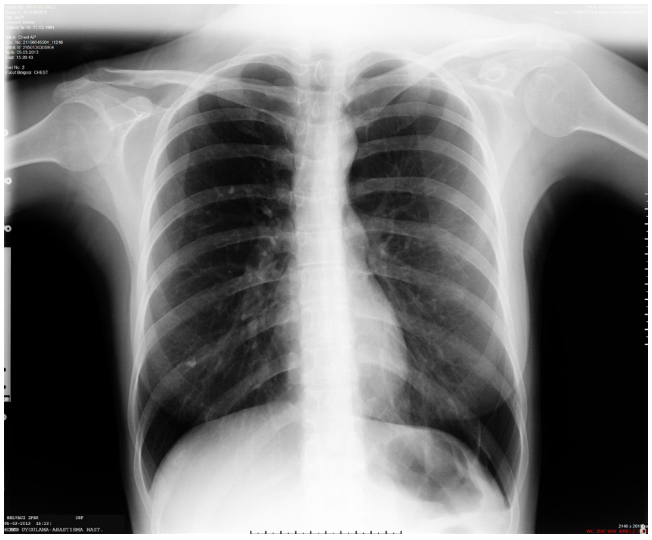


Figure 1. Postero-anterior chest x-ray of the patient in emergency service

Patient was hospitalized and nasal oxygen was administered at 3 lt/min. Her pleuritic chest pain diminished and lung auscultation sounds were normal on follow-up. PA chest x-ray control revealed left lung was completely expanded and no pneumothorax was found. She was discharged on her fourth day. Her control examination 1 week later was normal. She re-admitted to our outpatient clinics approximately 3 months after her first admission with similar complaints. Her history revealed that her complaints started during menstrual period. Physical examination revealed diminished left apical lung auscultation sounds. Left sided recurrent spontaneous pneumothorax was found in PA chest x-ray. She was hospitalized again and left VATS apical wedge resection and left apical pleurectomy was performed. Neither diaphragmatic pores nor lesions compatible with thoracic endometriosis in left hemi-thorax were found during the operation. Multiple biopsies from the parietal pleura of the left hemi-thorax were performed in order to find thoracic endometriosis. Pathologic examination did not reveal endometriosis. Apical wedge resection material was also examined by pathology department and reported as bullous emphysema. Air drainage has stopped at the fourth postoperative day. Physical examination and the PA chest x-ray was normal. Thoracic drain was removed at the same day. Patient was consulted to the gynecology clinics and oral contraceptive including 2 mg of dienogest was administered. She was discharged at the fifth postoperative day. Her control examination 1 week later was normal (Figure 2).

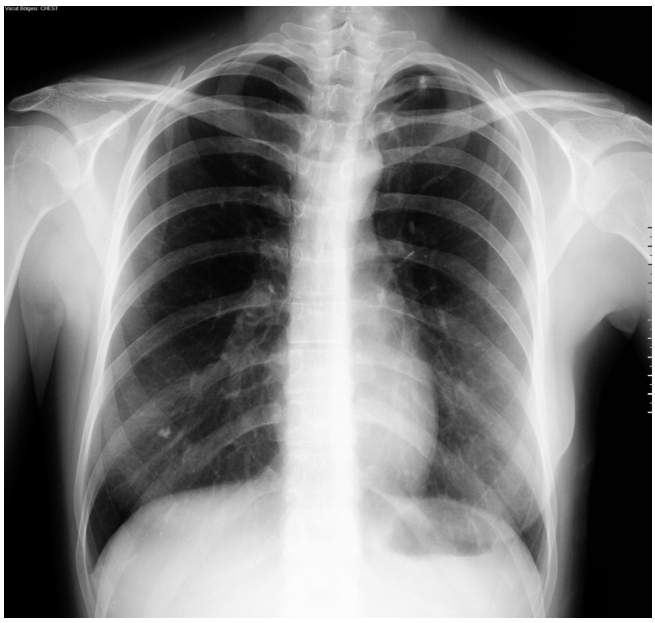


Figure 2. Post-operative postero-anterior chest x-ray of the patient 1 week later

She re-admitted to our hospital's emergency department clinics approximately 2 months after her first admission with same complaints. Her medical history revealed that she stopped taking the oral contraceptives willingly because she was planning for pregnancy. Physical examination revealed diminished left apical lung auscultation sounds. Left sided recurrent spontaneous pneumothorax was found in PA chest x-ray. Patient was hospitalized and nasal oxygen was administered at 3lt/min. Patient was consulted to the gynecology clinics and was administered oral contraceptives including 2 mg of cyproterone acetate and 0,035 mg of ethinyl estradiol. Physical examination and the PA chest x-ray at the fourth day of hospitalization was normal. She was discharged at the same day. Oral contraceptive therapy continued for 6 months because of recurrent pneumothorax. The patient is in her follow-up period for almost 2 years and she did not have a recurrent pneumothorax episode.

Discussion

CP is a special type of pneumothorax related with the menstrual period that can only be seen in women because of its pathophysiological mechanism and is usually misdiagnosed. There are two etiological factors that are blamed in the pathophysiology of CP. First one is thoracic endometriosis and the second is single or multiple diaphragmatic pores. Our patient was infertile which supported the diagnosis of endometriosis but we could not find any endometrial tissue within the thorax or pores on the diaphragm during the videothoracoscopic examination. Pathological examination of the pleural biopsies that were obtained during the surgery did not reveal any endometriosis or diaphragmatic pores despite the fact that diaphragmatic pores can be seen in 23-88% of the patients and endometriosis usually accompanies with these pores [4]. The treatment of CP consists of both medical and surgical treatment. First line of surgical treatment is exploration of thorax via VATS and revealing the pathophysiological factors of CP. It consists of wedge resection of lung parenchyma that includes the endometriotic tissue and pleurectomy for pleural endometriosis. Diaphragmatic defects should be sutured if present and if there are numerous pores that cannot be repaired by suturing, surgeon should perform partial or total diaphragmatic resection and reconstruction. Despite these surgical treatment techniques postoperative recurrence rates of CP is 30% [5]. Our patient had a recurrent episode of CP 2 months after surgery despite that she had undergone videothoracoscopic apical wedge resection and apical pleurectomy. Because of high incidences of postoperative recurrence, medical treatment should be combined with the surgical treatment. Gonadotropic hormone analogues should be administered to the patients for 3-6 months in order to allow the pleurodesis to take effect [6]. Our patient had a recurrent episode of CP after she stopped taking her medical treatment that only lasted for a month. This shows the importance of medical treatment in CP. Our patient had no recurrences for 2 years after she completed her medical treatment that lasted 6 months. It is tenable that the combination of medical with surgical treatment prevents recurrences in CP. But proper history taking as in our case prevents unnecessary surgical procedures and helps in selecting the optimum medical treatment strategy.

In conclusion, CP causes recurrences even after the surgery. Medical treatment is successful in preventing the recurrences. Physicians should question that if the patients are taking their medical treatment regularly before deciding that the surgical treatment failed in recurrent pneumothorax.

Declaration of conflicting interests

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

Funding

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

References

1. Visouli AN, Zarogoulidis K, Kougioumtzi I, Huang H, Li Q, Dryllis G, et al. Catamenial pneumothorax. J Thorac Dis 2014; 6: S448-60.
2. Baoquan L, Liangjian Z, Qiang W, Hai J, Hezhong C, Zhiyun X. Catamenial pneumothorax associated with multiple diaphragmatic perforations and pneumoperitoneum in a reproductive woman. J Formos Med Assoc 2014; 113: 385-7.
3. Alifano M, Trisolini R, Cancellieri A, Regnard JF. Thoracic endometriosis: current knowledge. Ann Thorac Surg 2006; 81: 761-9.
4. Joseph J, Sahn SA. Thoracic endometriosis syndrome: new observations from an analysis of 110 cases. Am J Med 1996; 100: 164-70.
5. Baysungur V, Tezel C, Okur E, Yılmaz B. Recurrent pneumothorax diagnosed as catamenial after videothoracoscopic examination of the pleural cavity. Surg Laparosc Endosc Percutan Tech 2011; 21: 81-3.
6. Leong AC, Coonar AS, Lang-Lazdunski L. Catamenial pneumothorax: surgical repair of the diaphragm and hormone treatment. Ann R Coll Surg 2006; 88: 547-9.

Current Thoracic Surgery

To cite this article: Stamenovic D. Bronchoscopic management of bronchopleural fistula. Curr Thorac Surg 2016;1(1):38-43.

Review Article

Bronchoscopic management of bronchopleural fistula

Davor Stamenovic[a]

Department of Thoracic Surgery, St. Vincentus Kliniken, Germany

ABSTRACT

Bronchopleural fistula (BPF) represents a pathological communication between any part of bronchial tree and the pleural space. Mostly it is a rare yet serious complication of different pulmonary conditions like certain infections, trauma, malignancy and/or surgery, going along with significant mortality reported to be as high as 58%. Diagnosis of BPF is mostly done by evaluating these three data: clinical appearance, bronchoscopy and CT scan. The treatment of BPF may initially differ according to the time of appearance as well as clinical presentation. As most BPF goes along with empyema, it is, obviously, necessary to deal with it. This is most commonly achieved with a chest tube. Conservative management of BPF can be achieved using a significant variety of materials and methods with reportedly moderate to excellent results in the treatment of etiologically and sizably different BPF. Methyl-2-cyanoacrylate, fibrin sealant together with spongy calf bone, polidocanol - hydroxypolyethoxidodecane, amplatzer device, silver nitrate, stenting and endobronchial valves have all been employed in bronchoscopic treatment of a BPF. There is no evidence based guideline for its management, either surgically or endoscopically. The treatment of choice is always in the hands of the physician, preferably armed with the current knowledge and capacity of utilizing it.

Keywords: Bronchopleural fistula; bronchial fistula; bronchoscopy; pleural disease; empyema; surgery

Corresponding Author[a]: Davor Stamenovic, MD. Department of Thoracic Surgery, St. Vincentus Kliniken, D- 76137 Karlsruhe, Germany
E-mail:davor.stamenovic@vicentius-ka.de

Received 05.09.2016 accepted 16.11.2016

Introduction

BPF represents a pathological communication between any part of bronchial tree and the pleural space. Although it could appear even idiopathic, mostly it is a rare yet serious complication of different pulmonary conditions like certain infections, trauma, malignancy and/or surgery, going along with significant mortality, which is reported to be as high as 58% [1].

BPF is thought to be most frequent after surgery [2], having a published overall incidence of 4.4% after major anatomical resections [3], being as high as 20% after pneumonectomy [4]. Predisposing factors for development of BPF may be: immunosuppression, neoadjuvant tumor therapy, presence of pulmonary infection in the time of surgery and active smoking. Also surgical technique may have certain importance on avoiding it [5].

Also it is well known that certain surgical procedures, such as right sided pneumonectomy or right lower lobectomy, go along with increased risk for developing BPF.

Modern radio- and chemotherapy therapies for lung cancer as well as necrotic lung infections may add significantly to overall morbidity from BPF. Furthermore, some other conditions, like ARDS, or even Boerhaave Syndrome could also be responsible for it BPF development.

Surgical BPF can be generally classified according to the time of occurrence as "early" if it occurs in up to 7 days after surgery, "intermediate" if it appears in the time between 8 and 30 days following surgery and, finally, "late" after that period [6].

Diagnosis of BPF is mostly done by evaluating these three data: clinical appearance, bronchoscopy and CT scan. Rarely additional procedures like instillation of methylene blue and its visualisation in the chest tube can be needed.

Treatment

The treatment of BPF may initially differ according to the time of appearance as well as clinical presentation. If it appears acute, especially with life threatening conditions like flooding of the contralateral lung and respiratory insufficiency, the measures must be taken to clear the airway paths and to decompress involved hemithorax with a chest tube.

As most BPF goes along with empyema, it is, obviously, necessary to deal with it. This is most commonly achieved with a chest tube. Moreover it is often required to treat debilitation and multiple comorbidities, which often accompanies BPF.

Accepting that each of the procedures has its own benefits and misfits, surgical repair has had historically bigger role in handling "surgical" BPF, especially with "earlies", up to 7th postoperative day. Different surgical procedures have been involved in dealing with this problem: rethoracotomy with bronchial stump closure and covering with some of the thoracic wall muscles or omentum, sternotomy with the same idea, thoracoplasty either staged or not, fenestration or simple chest tube as a long term therapy. Some of these procedures being rather aggressive are not well tolerated by all BPF patients.

Conservative management of BPF can be achieved using a significant variety of materials and methods that could be employed with reportedly moderate to excellent results in the treatment of etiologically and sizably different BPF.

Bronchoscopic Treatment of Bronchopleural Fistula

The first two reported successful bronchoscopic management of BPF were published back in 1977 by two independent groups, Ratliff et al. [7] and Hartmann et al. [8] respectively. Both of them described their single case of peripheral BPF successfully closed using a sterilized fishing weight to block previously identified (sub) segmental bronchus in the first and using tissue glue, methyl-2-cyanoacrylate, and simply filling up segmental bronchi of a right upper lobe in the second case.

Almost twenty years later, the same material, methyl-2-cyanoacrylate, was successfully employed in closing up of 10 out of 12 central BPF up to 0.5 cm [9]. The glue firms after 10 seconds, so it was relatively easy to keep it in situ. Apart from them, other groups have also successfully treated this problem in a similar way with different success rates and published their experiences as case reports [10-12].

Another landmark study describing a novel technique for closing central BPF dates back in 1998 [13]. Hollaus et al. employed either only fibrin sealant, for the BPF 3 mm or less, or together with spongy calf bone, which was stuck in the fistula minimizing the orifice and preventing dislocation of the fibrin glue into the pleural cavity . The overall rate of successful fistula closure was 35.6%. Fistulas bigger than 8mm were not considered for endoscopic closure.

Varoli et al. in 1998 [14] published their study describing another method in closing central BPF. They successfully treated 23 out of 35 consecutive patients

with central postresectional BPF with multiple and repeatedly submucosal injections of polidocanol - hydroxypolyethoxidodecane (Aethoxysklerol Kreussler) on the margins of the fistula. In contrast to other methods, they managed to close fistula up to 10mm diameter.

The next big step in bronchoscopic handling of both central and peripheral BPF was made in 2008 with an article published by Kramer et al. [15]. They used Amplatzer device (AD) to close 5 mm large central postresectional BPF in two of their patients. Amplatzer device has been developed and used mostly either for treatment of congenital heart disorders or, in case of the vascular plug, endovascular catheter embolization of abnormal vascular communication. Both are easily applicable and available in different sizes. ASD-occluder has a central waist from 4-40 mm and disks on both sides of it, which are at least 10mm larger. Amplatzer vascular plug is available in sizes from 4-16 mm, but in at least three different shapes. While the size of the vascular plug is suitable for most working channels of modern fiberoptic bronchoscopes and thus could be easily delivered under optical guidance, ASD-occluder could be challenging. A larger case series was published later on, again by the same group [16]. They first introduced a guide wire through the fistula using bronchoscope. After bronchography to evaluate the shape and length of the fistula, they introduced a delivery sheath over the wire through the defect, than AD on the same fashion, positioning it at the end under bronchoscopic guidance by extruding the central waist in the defect, both of the disks laying on the opposite sides of it. Nine out of ten of the patients in their cohort have been successfully treated with this technique, the only one unsuccessful case was due to a failed anchoring of the device and it's falling into the pleural cavity. The same group published their results with vascular plug device, having five out five successful treatments [17]. Meanwhile there is a raising published evidence in terms of case reports supporting this method in the treatment of central BPF [18-20]. The largest successfully healed fistula was 12 mm in diameter. Our own experience however showed only limited success, having only two out of four BPF fistula completely closed without involvement of some additional procedure (Figures 1-3).

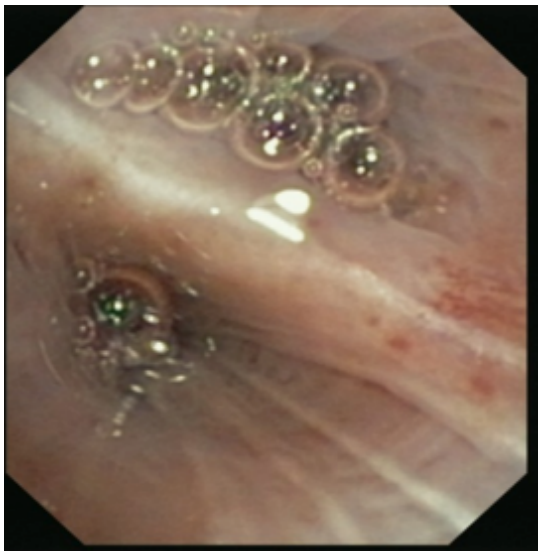


Figure 1. Peripheral BPF leading to lingula bronchus

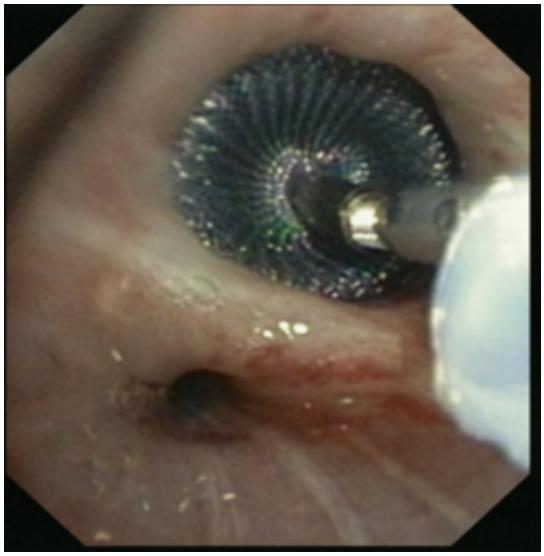


Figure 2. Introduction of the vascular plug (amplatzer) device through the flexible bronchoscope

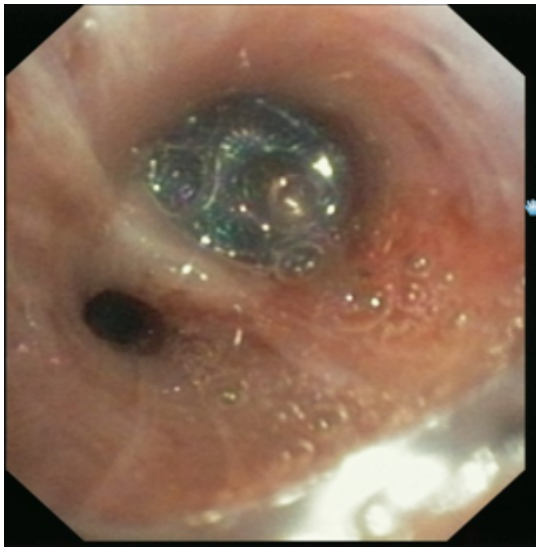


Figure 3. Successful occlusion of the BPF

Silver nitrate has been also employed as a tool for closing central BPF. In 2013 Boudaya et al. [6] published their series consisting of 17 patients treated with local application of silver nitrate. This application has had to be repeated until the fistula was closed. 16 patients was healed, the largest fistula was 9mm in diameter.

Endoscopic stenting as a solution for central BPF was promoted in 2001 by Watanabe et al. [21]. They used Dumon stents to cover central BPF after right upper lobectomy and failed attempt to close it surgically. From that point on there have been numerous case reports during past years with this particular type of stent having the same result, but also with some others, having different results. Koh et al. [22] successfully treated 20 mm large BPF after right upper lobe resection with the Dumon stent. Self-expandable metallic customized stent was employed as a temporary solution in treatment of seven post-pneumonectomy fistulas, the largest having a diameter of 12 mm [23]. The air leak ceased in all patients, in 43% of them surgery was successfully delayed, however overall mortality was 57%. Andreetti et al. [24] published their experience in management of post-pneumonectomy BPF. In their series of six patients having BPF up to 11 mm, but no empyema, they successfully treated all six of them by placing full covered self-expandable nitinol stents. The stents were removed after 71-123 days with completely cured BPF.

Another material frequently being employed in the treatment of BPF is endobronchial valves. The first successful case was published by Snell et al. in 2005 [25]. They closed a large peripheral BPF with a one-way valve, by positioning it in small segmental bronchi that was proved to be connected with the fistula. After that first report, other similar case reports with the same results were published [26,27]. In 2015 two series with valves were published. First study evaluated retrospectively the treatment of 21 patients, 19 of whom had peripheral BPF. None of those 19 patients tolerated water seal drainage system or even the ambulatory pleural drainage system well. 15 of 19 had prolonged air leak one week after treatment and 11 had it longer than two or more weeks. Two patients with central BPF had post-pneumonectomy fistula and were treated with the combination of a stent and a valve, one of them successfully, and the other unsuccessfully, followed by surgery [28]. The second study retrospectively enrolled 14 patients treated for peripheral BPF with overall success in six patients in the "medical group" (50%) and for eight in the "surgical group" (62.5%). Median time for air leak cessation in days for both groups was around 15 days [29].

Conclusion

As a conclusion, bronchopleural fistula is very serious complication of many medical conditions, however most frequently after surgery. There is no evidence based guideline for its management, either surgically or endoscopically.

Apart from the surgical management, which is more common given the relative higher frequency of the surgical patients among affected population with BPF, endoscopic management offers some benefits that should not be ignored. Not only it is less invasive, but in some occasions even more efficient than surgery. Avoiding the single anecdotal experience of endoscopic closing of either central or peripheral BPF with plethora of different materials and methods such as: blood clot, gel foam, antibiotics or cellulose without adequate published confirmation from other investigators later on, above mentioned endoscopic strategies have confirmed themselves as valid options in the treatment of BPF. Still not all are equally convenient for all types of BPF.

Central BPF, clearly visualized and measurable could be treated according to its diameter and location. Certainly proximal central BPF, like one after pneumonectomy or right upper lobe resection, with a diameter larger than 10 mm, reduces possibilities to stenting or placing AD. Left sided lobar BPF as well as BPF of the lower lobes on the right, especially if big, may be not amenable for stenting, thus leaving AD as the only method of choice.

Smaller BPF, regardless of the position, may involve other relatively successful tools like silver nitrate or polidocanol - hydroxypolyethoxidodecane, later being challenging, given the fact that, although published as a cohort, it has never been proven by other investigators but only one, unlike silver nitrate, stents or AD.

For the centrally located BPF smaller than 5 mm in diameter, the solid options can be either methyl-2-cyanoacrylate or amplatzer vascular plug and for the smallest fistulas even fibrin glue with or without calf bones.

Peripheral BPF are often treated by existing chest tube either only with suction/no suction combination or installation of certain chemicals or materials. Endoscopic treatment may be efficient as well, in the first place with endobronchial valves. However even this op-

tion does not offer a very good efficacy when compared to its risks. Another tool for treatment of peripheral BPF may be amplatzer vascular plug, though once epithelized, it is not removable anymore.

The treatment of choice is always in the hands of the physician, preferably armed with the current knowledge and capacity of utilizing it.

Declaration of conflicting interests

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

Funding

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

References

1. Uramoto H, Hanagiri T. The development of bronchopleural fistula in lung cancer patients after major surgery: 31 years of experience with 19 cases. Anticancer Res 2011; 31: 619-24.
2. Lois M, Noppen M. Bronchopleural fistulas: an overview of the problem with special focus on endoscopic management. Chest 2005;128:3955-65.
3. Sirbu H, Busch T, Aleksic I, Schreiner W, Oster O, Dalichau H. Bronchopleural fistula in the surgery of non-small cell lung cancer: incidence, risk factors, and management. Ann Thorac Cardiovasc Surg 2001; 7: 330-6.
4. Cerfolio RJ. The incidence, etiology, and prevention of postresectional bronchopleural fistula. Semin Thorac Cardiovasc Surg 2001; 13: 3-7.
5. al-Kattan K, Cattelani L, Goldstraw P. Bronchopleural fistula after pneumonectomy for lung cancer. Eur J Cardiothorac Surg 1995; 9: 479-82.
6. Boudaya MS, Smadhi H, Zribi H, Mohamed J, Ammar J, Mestiri T, et al. Conservative management of postoperative bronchopleural fistulas. J Thorac Cardiovasc Surg 2013; 146: 575-9.
7. Ratliff JL, Hill JD, Tucker H, Fallat R. Endobronchial control of bronchopleural fistulae. Chest 1977; 71: 98-9.
8. Hartmann W, Rausch V. New therapeutic application of the fiberoptic bronchoscope. Chest 1977; 71: 237.
9. Scappaticci E, Ardissone F, Ruffini E, et al. Postoperative bronchopleural fistula: endoscopic closure in 12 patients. Ann Thorac Surg 1994; 57: 119-22.
10. Roksvaag H, Skalleberg L, Nordberg C, Solheim K, Hoivik B. Endoscopic closure of bronchial fistula. Thorax 1983;38: 696-7.
11. Torre M, Chiesa G, Ravini M, Vercelloni M, Belloni PA. Endoscopic gluing of bronchopleural fistula. The Ann Thorac Surg 1987; 43:295-97.
12. Wood RE, Lacey SR, Azizkhan RG. Endoscopic management of large, postresection bronchopleural fistulae with methacrylate adhesive (Super Glue). J Pediatr Surg 1992; 27: 201-2.
13. Hollaus PH, Lax F, Janakiev D, Lucciarini P, Katz E, Kreuzer A, et al. Endoscopic treatment of postoperative bronchopleural fistula: experience with 45 cases. Ann Thorac Surg 1998; 66: 923-7.
14. Varoli F, Roviaro G, Grignani F, Vergani C, Maciocco M, Rebuffat C. Endoscopic treatment of bronchopleural fistulas. Ann Thorac Surg 1998; 65: 807-9.
15. Kramer MR, Peled N, Shitrit D, Atar E, Saute M, Shlomi D, et al. Use of Amplatzer device for endobronchial closure of bronchopleural fistulas. Chest 2008; 133: 1481-4.
16. Fruchter O, Kramer MR, Dagan T, Raviv Y, Abdel-Rahman N, Saute M, et al. Endobronchial closure of bronchopleural fistulae using amplatzer devices: our experience and literature review. Chest 2011; 139: 682-7.
17. Fruchter O, Bruckheimer E, Raviv Y, Rosengarten D, Saute M, Kramer MR. Endobronchial closure of bronchopleural fistulas with Amplatzer vascular plug. Eur J Cardiothorac Surg 2012; 41: 46-9.
18. Scordamaglio PR, Tedde ML, Minamoto H, Pedra CA, Jatene FB. Endoscopic treatment of tracheobronchial tree fistulas using atrial septal defect occluders: preliminary results. J Bras Pneumol 2009; 35: 1156-60.

19. Gulkarov I, Paul S, Altorki NK, Lee PC. Use of Amplatzer device for endobronchial closure of bronchopleural fistulas. Interact Cardiovasc Thorac Surg 2009; 9: 901-2.

20. Klotz LV, Gesierich W, Schott-Hildebrand S, Hatz RA, Lindner M. Endobronchial closure of bronchopleural fistula using Amplatzer device. J Thorac Dis 2015; 7: 1478-82.

21. Watanabe S, Shimokawa S, Yotsumoto G, Sakasegawa K. The use of a Dumon stent for the treatment of a bronchopleural fistula. Ann Thorac Surg 2001; 72: 276-8.

22. Koh MS, Ling Hsu AA, Thirugnanam A. Novel management of a large chronic bronchocutaneous fistula after lobectomy. Interact Cardiovasc Thorac Surg 2005; 4: 248-9.

23. Dutau H, Breen DP, Gomez C, Thomas PA, Vergnon JM. The integrated place of tracheobronchial stents in the multidisciplinary management of large post-pneumonectomy fistulas: our experience using a novel customised conical self-expandable metallic stent. Eur J Cardiothorac Surg 2011; 39: 185-9.

24. Andreetti C, D'Andrilli A, Ibrahim M, Ciccone AM, Maurizi G, Mattia A, et al. Effective treatment of post-pneumonectomy bronchopleural fistula by conical fully covered self-expandable stent. Interact Cardiovasc Thorac Surg 2012; 14: 420-3.

25. Snell GI, Holsworth L, Fowler S, Ericksson L, Reed A, Daniels FJ, et al. Occlusion of a broncho-cutaneous fistula with endobronchial one-way valves. Ann Thorac Surg 2005; 80: 1930-2.

26. Toma TP, Kon OM, Oldfield W, Sanefuji R, Griffiths M, Wells F, et al. Reduction of persistent air leak with endoscopic valve implants. Thorax 2007; 62: 830-3.

27. Schweigert M, Kraus D, Ficker JH, Stein HJ. Closure of persisting air leaks in patients with severe pleural empyema--use of endoscopic one-way endobronchial valve. Eur J Cardiothorac Surg 2011; 39: 401-3.

28. Reed MF, Gilbert CR, Taylor MD, Toth JW. Endobronchial valves for challenging air leaks. Ann Thorac Surg 2015; 100: 1181-6.

29. Hance JM, Martin JT, Mullett TW. Endobronchial valves in the treatment of persistent air leaks. Ann Thorac Surg 2015; 100: 1780-5; discussion 85-6.

Current Thoracic Surgery

To cite this article: Bugalho A, Rozman A. Endobronchial ultrasound: a guide to mediastinal disorders. Curr Thorac Surg 2016;1(1): 44-54.

Review Article

Endobronchial ultrasound: a guide to mediastinal disorders

António Bugalho[1,2a], Ales Rozman[3]

[1]Department of Pulmonology, CUF Infante Santo Hospital, CUF Descobertas Hospital, Lisbon, Portugal
[2]Chronic Diseases Research Center, NOVA Medical School, NOVA University of Lisbon, Portugal
[3]Department of Interventional Pulmonology, University Clinic Golnik, Golnik, Slovenia

ABSTRACT

In the last decade endobronchial ultrasound with real-time guided needle aspiration (EBUS-NA) has been recognized worldwide as a tool with remarkable impact on routine clinical practice. In the present review article, we focus on specific disease-related features of EBUS-NA, including diagnosis and staging of thoracic malignancies, sarcoidosis, tuberculosis and its role in the evaluation of isolated enlarged mediastinal lymph nodes. We also address some less common conditions and discuss emerging and future developments in EBUS technique.

Keywords: Interventional ultrasonography; bronchoscopy; mediastinum; neoplasms; thoracic disease; sarcoidosis; tuberculosis

Corresponding Author[a]: António Bugalho, MD. Chronic Diseases Research Center, NOVA Medical School, NOVA University of Lisbon, Portugal.
Email: antonio.bugalho@jmellosaude.pt

Received 16.06.2016 accepted 15.07.2016

Introduction

The mediastinum is an important anatomic region, which contains many vital structures and represents one of the main areas of interest for the Pulmonologist and the Thoracic Surgeon.

Several disease processes can affect different mediastinal structures where prompt and accurate diagnosis has a direct impact on treatment and prognosis. In the last decade, convex probe endobronchial ultrasound (CP-EBUS) with real-time guided needle aspiration (NA) has been accepted worldwide as a valuable tool with tremendous impact on routine clinical practice [1-3] (Figure 1). The equipment can be introduced into the airway or in the esophagus as an alternative mediastinal transport pathway as far as the left suprarenal gland [4-7]. The invasiveness of the procedure is much lower than concurrent techniques and EBUS-NA is feasible on outpatient basis under local anesthetic and moderate sedation [8]. A high diagnostic yield and very low complication rate contribute to establish EBUS-NA as the first-choice diagnostic tool in numerous mediastinal disorders [9].

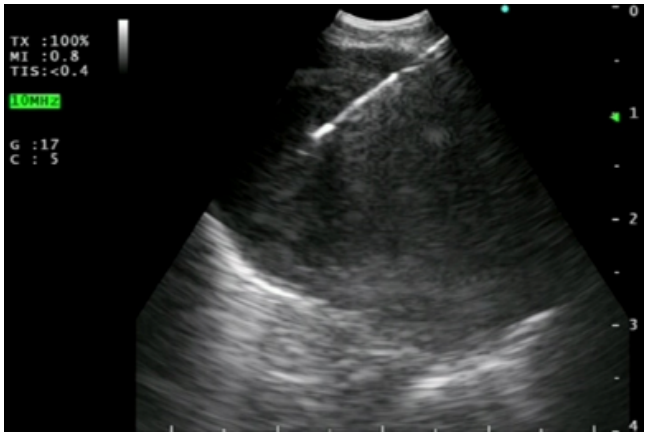


Figure 1. EBUS guided puncture of a mediastinal lymph node

EBUS-NA is most often used in lung cancer staging, for definitive tissue diagnosis in central malignant lesions or for diagnosis of other tumors with its origin or spread into the mediastinum. The obtained specimens can be processed for immunocytochemistry and DNA analysis [10]. Additionally, EBUS-NA provides useful diagnostic samples, including microbiology, for many benign diseases. B-mode and Doppler technique support the selection of the best biopsy spot, or in certain cases, provide complementary data for alternative diagnosis [11-14] (Figure 2).

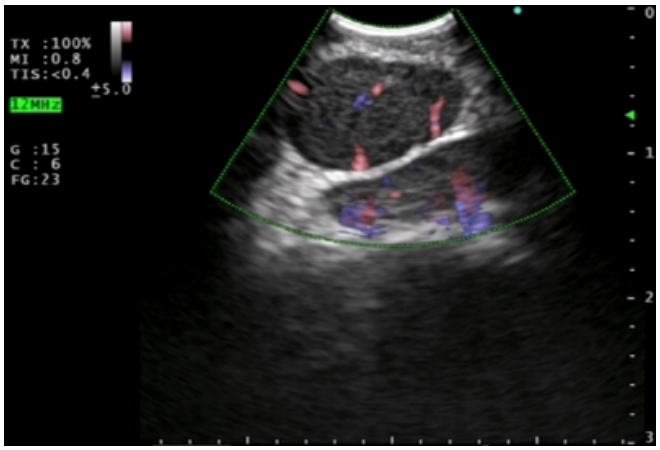


Figure 2. Assessment of mediastinal lymph nodes Doppler vascular pattern

The CP-EBUS instrument and NA technique were already described in detail in countless previous publications [15]. Therefore, in this article, we focus on specific disease-related features of CP-EBUS, including diagnosis and staging of thoracic malignancies, sarcoidosis, tuberculosis and its role in the evaluation of isolated enlarged mediastinal lymph nodes. We also address some less common conditions and discuss emerging developments in CP-EBUS technique.

Lung Cancer Diagnosis

The standard approach to lung cancer diagnosis comprises non-invasive imaging tests followed by invasive procedures such as flexible bronchoscopy or CT-guided transthoracic needle aspiration (CT-TTNA). The selected technique should offer maximum information regarding diagnosis (and staging) with minimum risk to the patient. Flexible bronchoscopy has a high diagnostic yield for endobronchial tumors but for peripheral and extraluminal lesions its sensitivity is rather low [16]. Also, CT-TTNA carries a significant risk of complications especially in central and small lung or mediastinal lesions. In the past, some patients would remain without a definitive diagnosis despite extensive work-up and had to undergo surgical biopsy, not always suitable for those with advanced disease or significant comorbidities.

In the last few years, real-time EBUS-NA proved to be an important option to overcome this situation, and diagnose lung cancer in patients with centrally located tumors. Tournoy et al. [17] reported a sensitivity of 84% and Nakajima et al. [18] obtained 94.1% sensitivity and 94.3% diagnostic accuracy for EBUS-NA in the diagnosis of central lung lesions not visible during routine bronchoscopy. EUS-NA has also been used to diagnose

lung tumors abutting the esophagus [19].The choice between EBUS and EUS depends on the availability of equipment, expertise and the location of the suspicious lesion. In an observational study, combined CP-EBUS with CP-EUS-B (transesophageal endobronchial ultrasound) after failure of conventional techniques, provided a definitive diagnosis in 106 of 121 cases (87.6%) [20]. Dincer et al. [21] even demonstrated that it is feasible and safe to perform EBUS-NA or EUS-NA in ≥10mm lesions not adjacent to the tracheobronchial tree or the esophagus. Of mention, this should be tried only by highly trained operators since there is the potential for reduced yield and higher complications compared to the puncture of abutting lesions.

With endosonography there is also the potential of providing diagnosis and mediastinal staging in the same procedure. It is mandatory that the central tumor is sampled after all lymph nodes are punctured, to avoid needle contamination. In other cases, if the primary lesion cannot be easily assessed, tissue may be acquired from highly suspicious metastatic lymph nodes to diagnose lung cancer.

In 2015, a randomized controlled trial by Navani et al. [22] have shown that EBUS-NA as the initial investigation in diagnosis of suspected lung cancer lesions reduces the time to treatment decision, compared with flexible bronchoscopy or CT-TTNA.

Of mention, linear EBUS does not replace conventional techniques since its size, angulation and image quality do not allow a correct and complete inspection of the airways. Most physicians still use EBUS and the flexible bronchoscope as complementary tools in the same diagnostic procedure.

Lung Cancer Staging

The most common indication for EBUS-NA is lung cancer staging. Identification of metastatic lymph nodes is critical and influences treatment and prognosis. Imaging methods are not sufficiently sensitive to detect lymph node metastasis and in most cases a minimally invasive staging has to be performed. Recently, Ong et al. [23] have shown in N0 PET-CT patients a high false-negative rate detected by EBUS-NA. In a retrospective cohort of 15,316 patients with lung cancer, Ost et al. [24] concluded that when lymph node staging does not meet the international standard guidelines with mediastinal sampling first, patients undergo more diagnostic tests (some unnecessary) with greater morbidity.

Most guidelines recommend endosonography as the initial sampling method for mediastinal lymph node staging [1,25-27]. This is due to the fact that several systematic reviews and meta-analysis showed that EBUS-TBNA has a high pooled sensitivity (88-93%) [26,28-30]. Diagnostic accuracy is at least equivalent to cervical mediastinoscopy in the evaluation of mediastinal lymph node metastasis in lung cancer [31-32]. In a controlled trial, Yasufuku el al. [32] proved that there were no differences between CP-EBUS and mediastinoscopy regarding N stage (EBUS sensitivity, diagnostic yield and negative predictive value were 81%, 93% and 91% and mediastinoscopy 79%, 93% and 90% respectively).

Of notice, some EBUS-NA studies showed limitations regarding its negative predictive value (NPV). This means that a negative result should be further confirmed by other invasive methods especially if the pre-test probability is high [29,30]. Dooms et al. [33] showed that endosonography has an inadequate sensitivity to detect N1 disease in lung cancer (sensitivity of 38% was increased to 73% by adding mediastinoscopy). The risk of false-negative cases is higher if there is: a central tumor, primary tumor is ≥3cm, suspected N2 disease by PET-CT, proven N1 disease or tumor restaging following chemotherapy [1]. Staging by CP-EBUS plus EUS followed by surgical staging (in case of N0) compared to surgical staging alone resulted in higher sensitivity and avoided unnecessary thoracotomies [34,35].

Only in selected cases mediastinoscopy may be omitted and these negative cases should be subjected to follow-up [36].

Another important point regarding lung cancer staging is that all lymph node stations should be systematically investigated because targeted biopsy (guided by chest CT and/or PET scan) may downstage the patient [2]. Further studies are ongoing to test this hypothesis. Recent guidelines advise that at least three different mediastinal nodal stations (4R, 4L, 7) should be sampled in NSCLC patients with an abnormal mediastinum by CT or PET-CT [1].

Since EBUS-NA cannot assess all mediastinal stations it is recommended to be combined with EUS-NA for complete nodal staging [1]. One of the possible advantages of the EBUS scope is that it is officially approved in Europe to use in the upper digestive track. So, in a single procedure, with the same equipment, the operator can perform CP-EBUS and EUS-B [5,6,37] accessing most mediastinal and hilar lymph node stations (except station 5 and 6), improving diagnostic yield, decreasing the negative predictive value and reducing costs [1,38]. The drawback is that EBUS plus EUS-B may increase procedure time,

need prolonged sedation protocols, add complexity to the exam and require dedicated skills and training.

The available scientific data suggest that CP-EBUS should be undertaken first, followed by EUS-B [39] because adding EBUS to EUS increases accuracy (from 86.5% to 97.3%) and the opposite did not increase yield or sensitivity.

Since a single dedicated needle is used, N3 stations should be punctured first, followed by N2 and finally N1, to avoid upstaging. Each lymph node should be punctured at least 3 times [15] for cytological characterization and eventually molecular analysis (e.g. EGFR, ALK) [40].

An additional indication for CP-EBUS/EUS may be the detection and puncture of lung cancer metastases in the left adrenal gland. In a retrospective study by Crombag et al. [7] the CP-EBUS scope allowed the identification and transgastric puncture of this anatomic structure in the majority of lung cancer patients with signs of malignant involvement. Prospective data is needed to access feasibility and safety.

Lung Cancer Restaging

Selected studies have addressed the issue of restaging the mediastinum by endosonography. To downstage disease, stage III NSCLC patients may be submitted to neoadjuvant chemoradiotherapy. It is of utmost importance to identify the responders since they are able to benefit from subsequent surgery. Herth et al. [41] published the first EBUS-NA restaging study in lung cancer with an overall sensitivity of 76% and NPV of 20%. Other retrospective studies confirmed the lower sensitivity and NPV of EBUS mediastinal restaging compared to staging [42,43]. In 2015, a prospective trial combined CP-EBUS and EUS with a single echoendoscope for NSCLC restaging had an overall sensitivity, accuracy and NPV of 67%, 81% and 73%, respectively [4]. In view of these data, guidelines suggest that initial restaging may be performed by EBUS-TBNA and/or EUS-(B)-FNA for detection of persistent nodal disease but, if negative, subsequent surgical staging is indicated before radical surgery is attempted (grade C recommendation) [1].

Diagnosis of Extrathoracic Cancer

Patients with extrathoracic tumors may develop increased mediastinal or hilar lymph nodes. In most cases, there is the need to acquire material for correct diagnosis and staging. Different scenarios may occur: metastatic dissemination of the extrathoracic cancer, second malignancy, sarcoid-like reaction, reactive lymph nodes or benign disease (e.g. tuberculosis, sarcoidosis). Various authors reported the utility of EBUS-NA for differential diagnosis in patients with a previous extrathoracic malignancy [44-46]. A meta-analysis with 533 patients concluded that EBUS-NA has 85.6% diagnostic accuracy to detect mediastinal lymph node metastases of extrathoracic malignancies and 16% probability to have a negative result (these cases should be confirmed by more invasive methods) [47].

Lymphoma

In contrast with high diagnostic yield in lung cancer staging, diagnosis of lymphoma by EBUS-NA is somewhat less reliable [48]. The reason may lie in suboptimal size of biopsy specimens, obtained by dedicated 21G and 22G needles. A small observational study with 22G needles on 25 patients reported sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 90.9%, 100%, 100% and 92.6%, respectively [49]. In one case, additional mediastinoscopy was performed for further subtyping. Steinfort et al. reported 76% sensitivity with 22G needle, but surgical biopsy to define the subtype was required in 4 patients, which decreases the specificity of EBUS-NA for definitive diagnosis to 57% [50].

Rapid on-site evaluation of specimen is helpful to allocate more material to ancillary studies [48,51]. In suspicious cases, further sampling is needed to acquire enough material for immunophenotyping by flow cytometry and fluorescence in situ hybridization (FISH), which provide the basis for non-Hodgkin lymphoma (NHL) subclassification.

EBUS-NA provided diagnosis in 100% of relapsed lymphoma cases and an accurate alternative diagnosis in 97% of patients from the same group [52]. Sensitivity for subtyping to high-grade NHL, low-grade NHL and Hodgkin lymphoma in relapsed and de novo diagnosed patients was 90%, 100% and 79% respectively [52]. Grosu et al. were able to establish the diagnosis and subtype the lymphoma in 67% of new diagnosed patients and in 81% of relapsed lymphoma patients by EBUS-NA using 22G needle [53].

In conclusion, EBUS-NA may be used as an initial procedure for patients with suspected mediastinal lymphoma and may decrease the need for more invasive approaches [48,54,55]. Sensitivity for final diagnosis and subtyping varies, but is more reliable for relapsed than newly diagnosed patients [52,55,56]. Although EBUS-NA can reli-

ably provide alternative diagnosis, negative results do not completely exclude lymphoma [48,52,57,58].

Sarcoidosis

Most patients referred for evaluation of suspected pulmonary sarcoidosis present stage I or II disease, with increased lymphadenopaties. Flexible bronchoscopy with transbronchial lung biopsies (TBLB), endobronchial biopsies and non-guided needle aspiration have been the traditional method for diagnosis, when there is an indication for tissue confirmation. These sampling methods may be associated with adverse events such as bleeding or pneumothorax, especially in non-experienced hands. Instead, the detection of non-caseating granulomas can be easily and safely obtained by CP-EBUS or EUS in mediastinal and hilar lymph nodes (Figure 3).

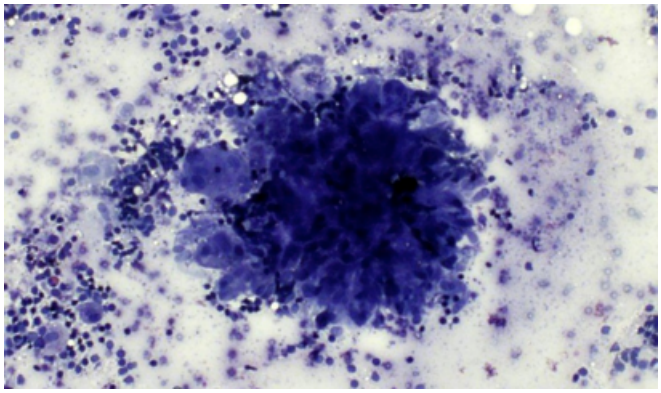


Figure 3. Non-caseating granuloma obtained by EBUS-NA in a patient with sarcoidosis

A randomized controlled trial published by Tremblay et al. [59] showed that EBUS-NA in patients with sarcoidosis is able to improve the diagnostic sensitivity in 22% compared to conventional TBNA. Another study [60], proved the enhanced diagnostic yield of EBUS/EUS (80%) versus bronchoscopy (53%) in sarcoidosis, although this trial did not include conventional TBNA. In 2014, Gupta et al. [61] demonstrated that individually EBUS-NA has the highest diagnostic yield (74.5%) and it is even better when combined with TBLB (90.9%) but the diagnostic yield of non-guided TBNA plus endobronchial biopsies and TBLB allows comparable results (85.5%, $P > 0.05$). In conclusion, EBUS/EUS may be the procedure of choice to diagnose sarcoidosis stage I and II, however those who do not have this equipment can still get a high diagnostic yield by combining the conventional techniques.

Tuberculosis

Intrathoracic tuberculosis lymphadenitis is a frequent companion of pulmonary tuberculosis and may as well represent a form of extrapulmonary tuberculosis on its own. The sputum smear for acid-fast bacilli and microbiological culture are still the mainstay of diagnosis, especially in the era of multi-drug resistant tuberculosis [62]. However, negative sputum, especially in the absence of pulmonary involvement represents a diagnostic challenge. Prompt histological diagnosis and isolation of tuberculosis bacilli was successfully achieved with 19G needles during standard TBNA procedure in HIV positive and negative patients with 83-87% sensitivity and 100% specificity [63,64]. EBUS-NA has an advantage of precise targeting the affected lymph nodes, but at the same time the disadvantage of thinner, 21G and 22G dedicated needles. Recent meta-analyses reported 80% pooled sensitivity and 100% specificity [65,66]. In all studies, 22G needles were used, except in Navani et al. where a combination of 21G and 22G needles had a sensitivity of 94% [67]. The culture and smear positive rates were 54% and 30% respectively [66]. Although the mycobacterium culture has a lower diagnostic yield than cytopathologic investigation, improves overall sensitivity from 72.7% to 95.4% [68]. The same applies to polymerase chain reaction of Mycobacterium tuberculosis from EBUS-NA samples, which increases diagnostic yield in addition to cytopathology and microbiology [69].

Isolated Enlarged Lymph Nodes

Mediastinal or hilar lymphadenopathy is a relatively common finding on chest CT-scans performed for various reasons. The term isolated mediastinal and hilar lymphadenopathy (IMHL) is defined as at least one enlarged lymph node in the mediastinum or hilus without evidence of lung nodule or mass or extrathoracic malignancy. The main diagnostic goal is to recognize a treatable condition like a granulomatous disorder (e.g. tuberculosis, sarcoidosis) or malignancy (e.g. lymphoma, metastasis or rare lymphoproliferative disorders) and to exclude patients with reactive lymph nodes associated with many chronic diseases (e.g. heart failure, bronchiectasis, chronic bronchitis, interstitial lung diseases, etc.) [70-74].

Although mediastinoscopy was a standard diagnostic procedure, recent the REMEDY clinical trial demonstrated, that EBUS-NA may be recommended as a first line investigation for IMHL [75]. EBUS-NA had 92% sensitivity and 40% negative predictive value for a treatable condition and spared mediastinoscopy in

87% of patients [75]. Moreover, the study also proved cost-effectiveness of such approach. EBUS-NA was also more accurate and cost-effective in comparison to classical TBNA [76]. However, the REMEDY trial, although prospective, found only 5% of patients with reactive lymphadenopathy, which might reflect some kind of preselection of patients referred to diagnostic work up [75].

Another single-center study found a much higher prevalence (48%) of reactive lymph nodes [77]. The presence of symptoms was not a reliable predictive factor for differentiation between reactive and pathological IMHL. EBUS-NA had an overall diagnostic accuracy and NPV of 91% and 84.2% respectively [77]. Therefore, the authors recommend surveillance, rather than further invasive procedures in the low risk group of older patients with comorbidities and with maximum lymph node diameter below 20mm, where the NPV may reach 93.8% [77].

Mediastinal Cysts

Mediastinal cysts may be classified as bronchogenic, pericardial, or enteric, depending on their lining epithelium. They are often punctured because of diagnostic uncertainty, although they have characteristic anechoic Doppler negative appearance on ultrasound examination [78] (Figure 4). EBUS guided real-time aspiration can be a therapeutic alternative to surgical resection [79,80]. Complications were reported in 16.1% of patients after EBUS-NA of the cyst, mostly as an infection [78,81]. Pericardial cysts are sometimes connected with pericardial sack and an infectious pericarditis might arise, either after intentional or accidental puncture [82, 83]. The use of prophylactic antibiotic should be considered before cyst puncture.

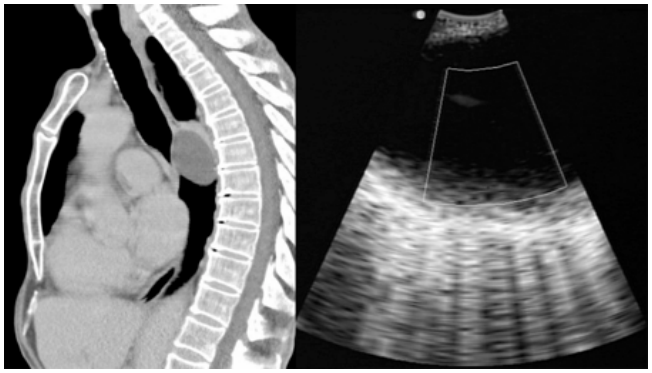


Figure 4. Anechoic Doppler negative mediastinal cyst

Future of CP-EBUS

CP-EBUS technique and applications are still under further development. New imaging techniques such as elastography may complement the procedure by better selection of the biopsy spot, which can result in more effective and less invasive diagnostic of mediastinal lesions and lung cancer staging [84-86] (Figure 5).

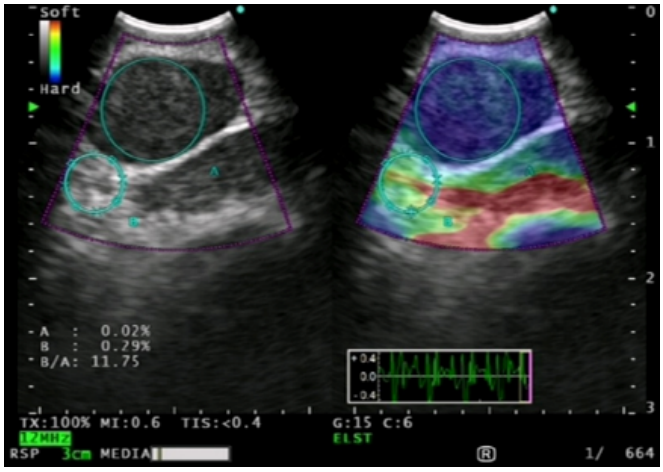


Figure 5. Elastography in a malignant lymph node

Novel 19G EBUS-NA needles were introduced and may further enhance the diagnostic yield, especially in detection and subtyping of lymphomas (Figure 6).

New EBUS bronchoscopes with higher resolution and smaller size of ultrasonic probe will reach deeper into the bronchial tree and into the upper lobes.

Combined CP-EBUS plus EUS-B procedure will become standard of care for lung cancer mediastinal staging in most interventional units.

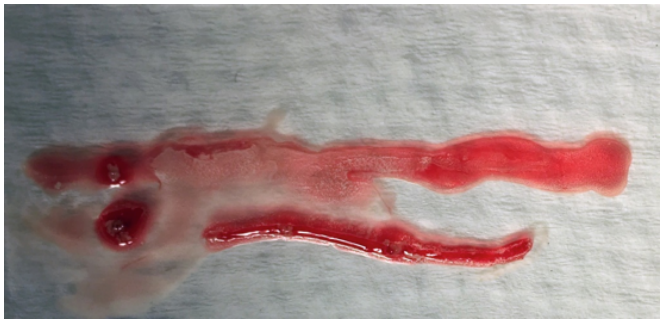


Figure 6. Histological material obtained with a dedicated 19G EBUS needle

Intra-tumoral delivery of cytostatic drugs by transbronchial guided needle injection may improve local control of recurrent central airway and mediastinal cancers, reducing doses and side effects [87-89].

There are also several none-conventional indications where CP-EBUS could occasionally be used, for instance the diagnosis of pulmonary embolism in patients with contraindication for intravenous contrast agent and for detection of non-thrombotic endovascular lesions [90].

Conclusion

As a conclusion, CP-EBUS resulted from the effort of innumerous investigators that believed that ultrasound imaging could be accomplished in the airways.

EBUS-NA and EUS-B-NA are now recommended as the first procedures for NSCLC lymph node staging. The technique has also clinical impact for lung cancer diagnosis and restaging of thoracic and extrathoracic malignancies.

In benign diseases, such as tuberculosis and sarcoidosis stage I/II EBUS-NA proved its added value by increasing diagnostic yield.

The international scientific community is still pursuing optimal performance as further studies are performed and new indications are tested. Structured learning programs and supervised training are essential to appropriately disseminate CP-EBUS.

Declaration of conflicting interests

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

Funding

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

References

1. Vilmann P, Clementsen PF, Colella S, Siemsen M, De Leyn P, Dumonceau JM, et al. Combined endobronchial and oesophageal endosonography for the diagnosis and staging of lung cancer. European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). Eur Respir J 2015; 46: 40-60.
2. Jenssen C, Annema JT, Clementsen P, Cui XW, Borst MM, Dietrich CF. Ultrasound techniques in the evaluation of the mediastinum, part 2: mediastinal lymph node anatomy and diagnostic reach of ultrasound techniques, clinical work up of neoplastic and inflammatory mediastinal lymphadenopathy using ultrasound techniques and how to learn mediastinal endosonography. J Thorac Dis 2015; 7: E439-58.
3. Slavova-Azmanova NS, Lizama C, Johnson CE, Ludewick HP, Lester L, Karunarathne S, et al. Impact of the introduction of EBUS on time to management decision, complications, and invasive modalities used to diagnose and stage lung cancer: a pragmatic pre-post study. BMC Cancer 2016; 28: 16: 44.
4. Szlubowski A, Zieliński M, Soja J, Filarecka A, Orzechowski S, Pankowski J, et al. Accurate and safe mediastinal restaging by combined endobronchial and endoscopic ultrasound-guided needle aspiration performed by single ultrasound bronchoscope. Eur J Cardiothorac Surg 2014; 46: 262-6.
5. Herth FJ, Krasnik M, Kahn N, Eberhardt R, Ernst A. Combined endoscopic-endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer. Chest 2010; 138: 790-4.
6. Hwangbo B, Lee GK, Lee HS, Lim KY, Lee SH, Kim HY, et al. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. Chest 2010; 138: 795-802.
7. Crombag LM, Annema JT. Left adrenal gland analysis in lung cancer patients using the endobronchial ultrasound scope: a feasibility trial. Respiration 2016; 91: 235-40.
8. Jeyabalan A, Medford AR. Endobronchial ultrasound-guided transbronchial needle aspiration: patient satisfaction under light conscious sedation. Respiration 2014; 88: 244-50.
9. Bonta PI, Crombag L, Annema JT. Linear endobronchial and endoesophageal ultrasound: a practice change in thoracic medicine. Curr Opin Pulm Med 2016; 22: 281-8.
10. Nakajima T, Anayama T, Koike T, Waddell T, Keshavjee S, Kimura H, et al. Simultaneous isolation of total RNA, DNA, and protein using samples obtained by EBUS-TBNA. J Bronchology Interv Pulmonol 2011; 18: 301-5.
11. Fujiwara T, Yasufuku K, Nakajima T, Chiyo M, Yoshida S, Suzuki M et al. The utility of sonographic features during endobronchial ultrasound-guided transbronchial needle aspiration for lymph node staging in patients with lung cancer: a standard endobronchial ultrasound image classification system. Chest 2010; 138: 641-7.
12. Nakajima T, Anayama T, Shingyoji M, Kimura H, Yoshino I, Yasufuku K. Vascular image patterns of lymph nodes for the prediction of metastatic disease during EBUS-TBNA for mediastinal staging of lung cancer. J Thorac Oncol 2012; 7: 1009-14.
13. Evison M, Morris J, Martin J, Shah R, Barber PV, Booton R, et al. Nodal staging in lung cancer: a risk stratification model for lymph nodes classified as negative by EBUS-TBNA. J Thorac Oncol 2015; 10: 126-33.
14. Memoli JS, El-Bayoumi E, Pastis NJ, Tanner NT, Gomez M, Huggins JT, et al. Using endobronchial ultrasound features to predict lymph node metastasis in patients with lung cancer. Chest 2011; 140: 1550-6.

15. Wahidi MM, Herth F, Yasufuku K, Shepherd RW, Yarmus L, Chawla M, et al. Technical Aspects of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: CHEST Guideline and Expert Panel Report. Chest 2016; 149: 816-35.
16. Rivera MP, Mehta AC, Wahidi MM. Establishing the Diagnosis of Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2013; 143: 142S-165S.
17. Tournoy KG, Rintoul RC, van Meerbeeck JP, Carroll NR, Praet M, Buttery RC, et al. EBUS-TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy. Lung Cancer 2009; 63:45-9.
18. Nakajima T, Yasufuku K, Fujiwara T, Chiyo M, Sekine Y, Shibuya K, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrapulmonary lesions. J Thorac Oncol 2008;3: 985-8.
19. Annema JT, Veseliç M, Rabe KF. EUS-guided FNA of centrally located lung tumours following a non-diagnostic bronchoscopy. Lung Cancer. 2005;48:357-61
20. Bugalho A, Ferreira D, Eberhardt R, Dias SS, Videira PA, Herth FJ, et al. Diagnostic value of endobronchial and endoscopic ultrasound-guided fine needle aspiration for accessible lung cancer lesions after non-diagnostic conventional techniques: a prospective study. BMC Cancer 2013; 13: 130.
21. Dincer HE, Gliksberg EP, Andrade RS. Endoscopic ultrasound and/or endobronchial ultrasound-guided needle biopsy of central intraparenchymal lung lesions not adjacent to airways or esophagus. Endosc Ultrasound 2015; 4: 40-3.
22. Navani N, Nankivell M, Lawrence DR, Lock S4, Makker H5, Baldwin DR, et al. Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomized controlled trial. Lancet Respir Med 2015; 3: 282-9.
23. Ong P, Grosu H, Eapen GA, Rodriguez M, Lazarus D, Ost D, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for systematic nodal staging of lung cancer in patients with N0 disease by computed tomography and integrated positron emission tomography-computed tomography. Ann Am Thorac Soc 2015; 12: 415-9.
24. Ost DE, Niu J, S Elting L, Buchholz TA, Giordano SH. Quality gaps and comparative effectiveness in lung cancer staging and diagnosis. Chest 2014; 145: 331-45.
25. Vansteenkiste J, De Ruysscher D, Eberhardt WE, Lim E, Senan S, Felip E, et al. Early and locally advanced nonsmall-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 (Suppl 6): vi89-vi98.
26. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging nonsmall cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143 (5 Suppl): e211S-e250S.
27. De Leyn P1, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for nonsmall-cell lung cancer. Eur J Cardiothorac Surg 2014; 45: 787-98.
28. Gu P, Zhao YZ, Jiang LY, Zhang W, Xin Y, Han BH. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. Eur J Cancer 2009; 45: 1389-96.
29. Adams K, Shah PL, Edmonds L, Lim E. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis. Thorax 2009; 64: 757-62.
30. Dong X, Qiu X, Liu Q, Jia J. Endobronchial ultrasound-guided transbronchial needle aspiration in the mediastinal staging of nonsmall cell lung cancer: a meta-analysis. Ann Thorac Surg 2013; 96: 1502-7.
31. Ernst A, Anantham D, Eberhardt R, Krasnik M, Herth FJ. Diagnosis of mediastinal adenopathy - real-time endobronchial ultrasoundguided needle aspiration versus mediastinoscopy. J Thorac Oncol 2008; 3: 577-82.
32. Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg 2011; 142: 1393-400.
33. Dooms C, Tournoy KG, Schuurbiers O, Decaluwe H, De Ryck F, Verhagen A, et al. Endosonography for mediastinal nodal staging of clinical N1 nonsmall cell lung cancer: a prospective multicenter study. Chest 2015; 147: 209-15.

34. Annema JT, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. JAMA 2010; 304: 2245-52.

35. Rintoul RC, Glover MJ, Jackson C, Hughes V, Tournoy KG, Dooms C, et al. Cost effectiveness of endosonography versus surgical staging in potentially resectable lung cancer: a health economics analysis of the ASTER trial from a European perspective. Thorax 2014; 69: 679-81.

36. Annema JT, De Leyn P, Clementsen P, Siemsen M, Vilmann P. Mediastinoscopy after negative endoscopic mediastinal nodal staging: can it be omitted? Eur Respir J 2015; 46: 1848-9.

37. Oki M, Saka H, Ando M, Tsuboi R, Nakahata M, Oka S, et al. Transbronchial vs transesophageal needle aspiration using an ultrasound bronchoscope for the diagnosis of mediastinal lesions: a randomized study. Chest 2015; 147: 1259-66.

38. Zhang R, Ying K, Shi L, Zhang L, Zhou L. Combined endobronchial and endoscopic ultrasound-guided fine needle aspiration for mediastinal lymph node staging of lung cancer: a meta-analysis. Eur J Cancer 2013; 49: 1860-7.

39. Kang HJ, Hwangbo B, Lee GK, Nam BH, Lee HS, Kim MS, et al. EBUS-centred versus EUS-centred mediastinal staging in lung cancer: a randomised controlled trial. Thorax 2014; 69: 261-8.

40. van der Heijden EH, Casal RF, Trisolini R, Steinfort DP, Hwangbo B, Nakajima T, et al. Guideline for the acquisition and preparation of conventional and endobronchial ultrasound-guided transbronchial needle aspiration specimens for the diagnosis and molecular testing of patients with known or suspected lung cancer. Respiration 2014; 88: 500-17.

41. Herth FJ, Annema JT, Eberhardt R, Yasufuku K, Ernst A, Krasnik M, et al. Endobronchial ultrasound with transbronchial needle aspiration for restaging the mediastinum in lung cancer. J Clin Oncol 2008; 26: 3346-50.

42. Szlubowski A, Herth FJ, Soja J, Kołodziej M, Figura J, Cmiel A, et al. Endobronchial ultrasound-guided needle aspiration in non-small-cell lung cancer restaging verified by the transcervical bilateral extended mediastinal lymphadenectomy: a prospective study. Eur J Cardiothorac Surg 2010; 37: 1180-4.

43. Nasir BS, Bryant AS, Minnich DJ, Wei B, Dransfield MT, Cerfolio RJ. The efficacy of restaging endobronchial ultrasound in patients with non-small cell lung cancer after preoperative therapy. Ann Thorac Surg 2014; 98: 1008-12.

44. Tournoy KG, Govaerts E, Malfait T, Dooms C. Endobronchial ultrasound-guided transbronchial needle biopsy for M1 staging of extrathoracic malignancies. Ann Oncol 2011; 22: 127-31.

45. Navani N, Nankivell M, Woolhouse I, Harrison RN, Munavvar M, Oltmanns U, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrathoracic lymphadenopathy in patients with extrathoracic malignancy: a multicenter study. J Thorac Oncol 2011; 6: 1505-9.

46. Parmaksız ET, Caglayan B, Salepci B, Comert SS, Kiral N, Fidan A, et al. The utility of endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal or hilar lymph node evaluation in extrathoracic malignancy: Benign or malignant? Ann Thorac Med 2012; 7: 210-4.

47. Yang B, Li F, Shi W, Liu H, Sun S, Zhang G, Jiao S. Endobronchial ultrasound-guided transbronchial needle biopsy for the diagnosis of intrathoracic lymph node metastases from extrathoracic malignancies: a meta-analysis and systematic review. Respirology 2014; 19: 834-41.

48. Nason KS, Kirchner A, Schuchert MJ, Luketich JD, Christie NA, Pantanowitz L, et al. Endobronchial ultrasound-transbronchial needle aspiration for lymphoma in patients with low suspicion for lung cancer and mediastinal lymphadenopathy. Ann Thorac Surg 2016; 101: 1856-63.

49. Kennedy MP, Jimenez CA, Bruzzi JF, Mhatre AD, Lei X, Giles FJ, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. Thorax 2008; 63: 360-5.

50. Steinfort DP, Conron M, Tsui A, Pasricha SR, Renwick WE, Antippa P, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the evaluation of suspected lymphoma. J Thorac Oncol 2010; 5: 804-9.

51. Ko HM, da Cunha Santos G, Darling G, Pierre A, Yasufuku K, Boerner SL, et al. Diagnosis and subclassification of lymphomas and non-neoplastic lesions involving mediastinal lymph nodes using endobronchial ultrasound-guided transbronchial needle aspiration. Diagn Cytopathol 2013; 41: 1023-30.

52. Moonim MT, Breen R, Fields PA, Santis G. Diagnosis and subtyping of de novo and relapsed mediastinal lymphomas by endobronchial ultrasound needle aspiration. Am J Respir Crit Care Med 2013; 188: 1216-23.

53. Grosu HB, Iliesiu M, Caraway NP, Medeiros LJ, Lei X, Jimenez CA, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis and subtyping of lymphoma. Ann Am Thorac Soc 2015; 12: 1336-44.

54. Korrungruang P, Oki M, Saka H, Kogure Y, Tsuboi R, Oka S, et al. Endobronchial ultrasound-guided transbronchial needle aspiration is useful as an initial procedure for the diagnosis of lymphoma. Respir Investig 2016; 54: 29-34.

55. Marshall CB, Jacob B, Patel S, Sneige N, Jimenez CA, Morice RC, et al. The utility of endobronchial ultrasound-guided transbronchial needle aspiration biopsy in the diagnosis of mediastinal lymphoproliferative disorders. Cancer Cytopathol 2011; 119: 118-26.

56. Iqbal S, DePew ZS, Kurtin PJ, Sykes AM, Johnson GB, Edell ES, et al. Endobronchial ultrasound and lymphoproliferative disorders: a retrospective study. Ann Thorac Surg 2012; 94: 1830-4.

57. Erer OF, Erol S, Anar C, Aydogdu Z, Ozkan SA. Diagnostic yield of EBUS-TBNA for lymphoma and review of the literature. Endosc Ultrasound 2016 Apr 28. doi: 10.4103/2303-9027.180762.

58. Senturk A, Babaoglu E, Kilic H, Hezer H, Dogan HT, Hasanoglu HC, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. Asian Pac J Cancer Prev 2014; 15: 4169-73.

59. Tremblay A, Stather DR, MacEachern P, Khalil M, Field SK. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. Chest 2009; 136: 340-46.

60. von Bartheld MB, Dekkers OM, Szlubowski A, Eberhardt R, Herth FJ, in 't Veen JC, et al. Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. JAMA 2013; 309: 2457-64.

61. Gupta D, Dadhwal DS, Agarwal R, Gupta N, Bal A, Aggarwal AN. Endobronchial Ultrasound Guided TBNA vs. Conventional TBNA in the diagnosis of sarcoidosis. Chest 2014; 146: 547-56.

62. Internal Clinical Guidelines Team (UK). Tuberculosis: Prevention, Diagnosis, Management and Service Organisation. London: National Institute for Health and Care Excellence (UK); 2016 Jan.

63. Bilaçeroğlu S, Günel O, Eriş N, Cağirici U, Mehta AC. Transbronchial needle aspiration in diagnosing intrathoracic tuberculous lymphadenitis. Chest 2004; 126: 259-67.

64. Harkin TJ, Ciotoli C, Addrizzo-Harris DJ, Naidich DP, Jagirdar J, Rom WN. Transbronchial needle aspiration in patients infected with HIV. Am J Respir Crit Care Med 1998; 157: 1913-8.

65. Ye W, Zhang R, Xu X, Liu Y, Ying K. Diagnostic efficacy and safety of endobronchial ultrasound-guided transbronchial needle aspiration in intrathoracic tuberculosis: a meta-analysis. J Ultrasound Med 2015; 34: 1645-50.

66. Li W, Zhang T, Chen Y, Liu C, Peng W. Diagnostic value of convex probe endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal tuberculous lymphadenitis: a systematic review and meta-analysis. Med Sci Monit 2015; 21:2 064-72.

67. Navani N, Molyneaux PL, Breen RA, Connell DW, Jepson A, Nankivell M, et al. Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy: a multicentre study. Thorax 2011; 66: 889-93.

68. Kiral N, Caglayan B, Salepci B, Torun Parmaksiz E, Fidan A, Comert SS, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in diagnosing intrathoracic tuberculous lymphadenitis. Med Ultrason 2015; 17: 333-8.

69. Eom JS, Mok JH, Lee MK, Lee K, Kim MJ, Jang SM, et al. Efficacy of TB-PCR using EBUS-TBNA samples in patients with intrathoracic granulomatous lymphadenopathy. BMC Pulm Med 2015; 15: 166.

70. Slanetz PJ, Truong M, Shepard JA, Trotman-Dickenson B, Drucker E, McLoud TC. Mediastinal lymphadenopathy and hazy mediastinal fat: new CT findings of congestive heart failure. AJR Am J Roentgenol 1998; 171: 1307-9.

71. Erly WK, Borders RJ, Outwater EK, Zaetta JM, Borders GT. Location, size, and distribution of mediastinal lymph node enlargement in chronic congestive heart failure. J Comput Assist Tomogr 2003; 27: 485-9.

72. Chabbert V, Canevet G, Baixas C, Galinier M, Deken V, Duhamel A, et al. Mediastinal lymphadenopathy in congestive heart failure: a sequential CT evaluation with clinical and echocardiographic correlations. Eur Radiol 2004; 14: 881-9.

73. Kirchner J, Kirchner EM, Goltz JP, Obermann A, Kickuth R. Enlarged hilar and mediastinal lymph nodes in chronic obstructive pulmonary disease. J Med Imaging Radiat Oncol 2010; 54: 333-8.

74. Kirchner J, Kirchner EM, Goltz JP, Lorenz VW, Kickuth R. Prevalence of enlarged mediastinal lymph nodes in heavy smokers - a comparative study. Eur Radiol 2011; 21: 1594-9.

75. Navani N, Lawrence DR, Kolvekar S, Hayward M, McAsey D, Kocjan G, et al. Endobronchial ultrasound-guided transbronchial needle aspiration prevents mediastinoscopies in the diagnosis of isolated mediastinal lymphadenopathy: a prospective trial. Am J Respir Crit Care Med 2012; 186: 255-60.

76. Grove DA, Bechara RI, Josephs JS, Berkowitz DM. Comparative cost analysis of endobronchial ultrasound-guided and blind TBNA in the evaluation of hilar and mediastinal lymphadenopathy. J Bronchology Interv Pulmonol 2012; 19: 182-7.

77. Evison M, Crosbie PA, Morris J, Martin J, Barber PV, Booton R. A study of patients with isolated mediastinal and hilar lymphadenopathy undergoing EBUS-TBNA. BMJ Open Respir Res 2014; 1: e000040.

78. Maturu VN, Dhooria S, Agarwal R. Efficacy and safety of transbronchial needle aspiration in diagnosis and treatment of mediastinal bronchogenic systs: systematic review of case reports. J Bronchology Interv Pulmonol 2015; 22: 195-203.

79. Twehues A, Islam S. Cystic lesions of the thorax: role of endobronchial ultrasound-guided transbronchial needle aspiration. J Bronchology Interv Pulmonol 2011; 18: 265-8.

80. Kirmani B, Kirmani B, Sogliani F. Should asymptomatic bronchogenic cysts in adults be treated conservatively or with surgery? Interact Cardiovasc Thorac Surg 2010; 11: 649-59.

81. Hong G, Song J, Lee KJ, Jeon K, Koh WJ, Suh GY, et al. Bronchogenic cyst rupture and pneumonia after endobronchial ultrasound-guided transbronchial needle aspiration: a case report. Tuberc Respir Dis (Seoul) 2013; 74: 177-80.

82. Haas AR. Infectious complications from full extension endobronchial ultrasound transbronchial needle aspiration. Eur Respir J 2009; 33: 935-8.

83. Lee HY, Kim J, Jo YS, Park YS. Bacterial pericarditis as a fatal complication after endobronchial ultrasound-guided transbronchial needle aspiration. Eur J Cardiothorac Surg 2015; 48: 630-2.

84. Izumo T, Sasada S, Chavez C, Watanabe J, Katsurada M, Matsumoto Y, et al. Endobronchial ultrasound elastography in the diagnosis of mediastinal and hilar lymph nodes. Jpn J Clin Oncol 2014; 44: 956-62.

85. Nakajima T, Inage T, Sata Y, Morimoto J, Tagawa T, Suzuki H, et al. Elastography for predicting and localizing nodal metastases during endobronchial ultrasound. Respiration 2015; 90: 499-506.

86. Rozman A, Malovrh MM, Adamic K, Subic T, Kovac V, Flezar M, et al. Endobronchial ultrasound elastography strain ratio for mediastinal lymph node diagnosis. Radiol Oncol 2015; 49: 334-40.

87. Khan F, Anker CJ, Garrison G, Kinsey CM. Endobronchial ultrasound-guided transbronchial needle injection for local control of recurrent nonsmall cell lung cancer. Ann Am Thorac Soc 2015; 12: 101-4.

88. Mehta HJ, Begnaud A, Penley AM, Wynne J, Malhotra P, Fernandez-Bussy S, et al. Treatment of isolated mediastinal and hilar recurrence of lung cancer with bronchoscopic endobronchial ultrasound guided intratumoral injection of chemotherapy with cisplatin. Lung Cancer 2015; 90: 542-547.

89. Hohenforst-Schmidt W, Zarogoulidis P, Darwiche K, Vogl T, Goldberg EP, Huang H, et al. Intratumoral chemotherapy for lung cancer: re-challenge current targeted therapies. Drug Des Devel Ther 2013; 7: 571-83.

90. Li P, Zheng W, Zhao L. Convex probe endobronchial ultrasound: applications beyond conventional indications. J Thorac Dis 2015; 7: E289-97.

CURRENT THORACIC SURGERY

Instructions for Authors

Aim and Scope

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

The Current Thoracic Surgery publishes articles in branches of general thoracic surgery, thoracic surgery anesthesia and thoracic disease (lung disease, esophagus disease).

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.

Being a peer-reviewed e-journal, the manuscripts sent will be evaluated by consultants and should be appropriate for the current version of common rules indicated for biomedical manuscripts as defined by the International Committee of Medical Journal Editors (ICMJE).

The journal accepts English language manuscripts. Articles will not be accepted for evaluation if they have been published or if they are considered for publication elsewhere and if they are not prepared according to the publication rules of the journal.

Peer Review Process

All manuscripts submitted for publication are strictly reviewed by at least three reviewers. Due to the Current Thoracic Surgery journal's double-blinded review principles, the names of the authors and reviewers are not known to the other.

Open Access Policy

The Journal has adopted the "open access policy" by considering the principle increasing the global exchange of the knowledge that generates useful results for humanity. The Current Thoracic Surgery is an "open access" e-journal the content of which is available to all users freely. Users can read the articles in full text, download, issue, print out and link to articles citing the journal without taking permission from the publisher or the author(s).

Archiving

This journal uses LOCKSS system to allow participating libraries create distributed permanent archives for conservation and restoration. If you would like more information about LOCKSS system.

Conflict of Interest Statement

Authors should declare as a statement at the end of the article 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 article.

Exclusive Publication Statement

Authors must certify that none of the material in the manuscript has been published previously in either print or electronic form, and that none of the submitted material is currently under consideration for publication elsewhere. This includes symposia, transactions, books, articles published by invitation, posting in electronic format and preliminary publications of any kind except an abstract of 400 words or fewer.

Ethics

Authors are responsible for all (ethical, scientific, legal, etc.) content of their published material.

Approval by the local institutional human research committee according to Helsinki Declaration is obligatory for experimental, clinical and drug researches. Informed consents from participants should be obtained and these two points should clearly be declared in the ''Materials and Methods'' section.

All papers reporting animal experiments should include a statement in ''Materials and Methods'' section giving assurance that all animals have received humane care in compliance with the Guide for the Care and Use of Laboratory Animals and indicating for the approval by the institutional ethical review board. If necessary, a copy of the form could be required by the editor. It is obligatory for the articles to be convenient in terms of research and publication ethics, the authors are responsible for their articles.

Informed Consent

Editors should protect the confidentiality of individual information (e.g. that obtained through the doctor–patient relationship). It is therefore almost always necessary to obtain written informed consent from patients described in case reports and for photographs of patients. It may be possible to publish without explicit consent if the report is important to public health (or is in some other way important); consent would be unusually burdensome to obtain; and a reasonable individual would be unlikely to object to publication (all three conditions must be met).

Open Access Policy

The journal has adopted the "open access policy" by considering the principle increasing the global exchange of the knowledge that generates useful results for humanity. Current Thoracic Surgery is an "open access" e-journal the content of which is available to all users freely. Users can read the articles in full text, download, issue, print out and link to articles citing the journal without taking permission from the publisher or the author(s).

Publication Frequency

The Current Thoracic Surgery is published three times annually.

Copyright Transfer

Authors of articles submitted to the Current Thoracic Surgery must transfer copyright to the journal during submission process. This transfer becomes binding upon acceptance of the article for publication. No part of the published material may be reproduced elsewhere without written permission from the Current Thoracic Surgery.

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 program 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).

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 plagiarism 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.

Reviewers; evaluate manuscripts based on content without regard to ethnic origin, gender, sexual orientation, citizenship, religious belief or political philosophy of the authors. They must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the Editor-in-Chief if they are aware of copyright infringement and plagiarism on the author's side. They must evaluate the submitted works objectively as well as present clearly their opinions on the works in a clear way in the review form. A reviewer who feels unqualified to review the research reported in a manuscript or knows that its prompt review will be impossible should notify the Editor-in-Chief and excuse himself from the review process.

Plagiarism Statement

Whether intentional or not, plagiarism is a serious violation. We define plagiarism as a case in which a paper reproduces another work with at least 25% similarity and without citation. In accordance with the code of conduct we will report any cases of suspected plagiarism or duplicate publishing. Current Thoracic Surgery reserves the right to use plagiarism detecting software to screen submitted papers at all times.

Article Download Statistics

The Current Thoracic Surgery provides article download statistics.

All manuscripts must be submitted through the online system for

TUBİTAK ULAKBİM DergiPark at http://dergipark.ulakbim.gov.tr/currthoracsurg/ (this URL will be available until the end of 2017 as declared bu ULAKBİM) or http://dergipark.gov.tr/currthoracsurg. You will be guided for uploading of the files.

Submission Process

Papers are accepted for publication on the understanding that they have not been published and are not going to be considered for publication elsewhere. Authors should certify that neither the manuscript nor its main contents have already been published or submitted for publication in another journal. The copyright release form, which can be found at web site must be signed by the corresponding author on behalf of all authors and must accompany all papers submitted. Please see the form for additional copyright details. After a manuscript has been submitted, it is not possible for authors to be added or removed or for the order of authors to be changed. If authors do so, their submission will be canceled.

Manuscripts may be rejected without peer review by the editor-in-chief if they do not comply with the instructions to authors or if they are beyond the scope of the journal. Any manuscript that does not conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, as reported at http://www.icmje.org/icmje-recommendations.pdf, will also be rejected. After a manuscript has been accepted for publication, i.e. after referee-recommended revisions are complete, the author will not be permitted to make changes that constitute departures from the manuscript that was accepted by the editor. Before publication, the galley proofs are always sent to the authors for corrections. Mistakes or omissions that occur due to some negligence on our part during final printing will be rectified in an errata section in a later issue. This does not include those errors left uncorrected by the author in the galley proof.

The use of someone else's ideas or words in their original form or slightly changed without a proper citation is considered plagiarism and will not be tolerated. Even if a citation is given, if quotation marks are not placed around words taken directly from another author's work, the author is still guilty of plagiarism. Reuse of the author's own previously published words, with or without a citation, is regarded as self -plagiarism. All manuscripts received are submitted to iThenticate®, a plagiarism checking system, which compares the content of the manuscript with a vast database of web pages and academic publications. Manuscripts judged to be plagiarized or self-plagiarized, based on the iThenticate® report or any other source of information, will not be considered for publication.

Preparation of Manuscript

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. Manuscripts should be written in English. Contributors who are not native English speakers are strongly advised to ensure that a colleague fluent in the English language or a professional language editor has reviewed their manuscript. Concise English without jargon should be used. Repetitive use of long sentences and passive voice should be avoided. It is strongly recommended that the text be run through computer spelling and grammar programs. Either British or American spelling is acceptable but must be consistent throughout.

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.

Manuscript Content

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.

Title and Contact Information

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 200 words must accompany each manuscript. The abstract must be structured to include the study's background and aim, materials and methods, results, and conclusions and keywords 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.

Introduction

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.

Results

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, Miyaz 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

Tables and Figures

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.

All tables and figures must have a caption and/or legend and be numbered (e.g., Table 1, Figure 2), unless there is only one table or figure, in which case it should be labeled "Table" or "Figure" with no numbering. Captions must be written in sentence case (e.g., Macroscopic appearance of the samples.). The font used in the figures should be Times New Roman. If symbols such as ×, μ, η, or ν are used, they should be added using the Symbols menu of Word.

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.

The resolution of images should not be less than 118 pixels/cm when width is set to 16 cm. Images must be scanned at 1200 dpi resolution and submitted in jpeg or tiff format. Graphs and diagrams must be drawn with a line weight between 0.5 and 1 point.

Graphs and diagrams with a line weight of less than 0.5 point or more than 1 point are not accepted. Scanned or photocopied graphs and diagrams are not accepted.

Charts must be prepared in 2 dimensions unless required by the data used. Charts unnecessarily prepared in 3 dimensions are not accepted.

Figures that are charts, diagrams, or drawings must be submitted in a modifiable format, i.e. our graphics personnel should be able to modify them. Therefore, if the program with which the figure is drawn has a "save as" option, it must be saved as *.ai or *.pdf. If the "save as" option does not include these extensions, the figure must be copied and pasted into a blank Microsoft Word document as an editable object. It must not be pasted as an image file (tiff, jpeg, or eps) unless it is a photograph.

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.

Privacy Statement

Names and e-mails will not be shared for any purpose.

Publisher

The "Current Thoracic Surgery" is the official e-journal of Turkish Society of Thoracic Surgery

Turkish Society of Thoracic Surgery (TSTS)

For more information, please contact

Berkant Özpolat, MD.

Professor of Thoracic Surgery

Editor-in-Chief of Current Thoracic Surgery

Email: berkantozpolat@yahoo.com

cts@tgcd.org.tr