Original Article

Primary mediastinal tumors in children and adults: a clinicopathological spectrum

Ariel A. Arteta[1,2]^, Vanessa Santiago-Pacheco[1,2], Juan C. Villada[3]

[1]Department of Pathology, University of Antioquia, Medellín, Colombia; [2]Grupo de Investigaciones en Patología Universidad de Antioquia (GRIP-UdeA), Medellín, Colombia; [3]Pediatric Oncology Department, Hospital San Vicente Fundación, Medellín, Colombia

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Correspondence to: Ariel A. Arteta, MD, PhD. Department of Pathology, University of Antioquia, Calle 67 # 52B-22 Block 13, Medellín, Colombia; Grupo de Investigaciones en Patología Universidad de Antioquia (GRIP-UdeA), Medellín, Colombia. Email: ariel.arteta@udea.edu.co.

Background: Mediastinal tumors are a heterogenous group of unrelated neoplasms that share the mediastinal anatomical location. There are no local publications regarding mediastinal masses, as such the clinical and pathological characteristics of this group of tumors in our population has been overlooked. The study aims to describe the mediastinal masses clinicopathological spectrum in children and adults.

Methods: With the objective to compare the clinicopathological spectrum of mediastinal tumors among children and adults we retrospectively review the medical charts and pathology reports of 110 patients with primary mediastinal masses between 2010 and 2022 at Hospital San Vicente Fundación and University of Antioquia pathology laboratory (Medellín, Colombia).

Results: We found statistically significant differences, regarding tumor location, tumor type, histological type and presenting complaint. The anterior mediastinal compartment was the most frequent location considering all tumors, with a statistically significant difference (P=0.042) favoring the adult group. A significant difference was also present in adults' anterior compartment for malignant tumors (P=0.02), which can be explained in both situations by the exclusive incidence of thymic tumors in the adult's anterior compartment. In contrast, malignant tumors show statistically significant differences (P=0.001) in the posterior compartment of the child group, associated with the high incidence of neurogenic tumors in this group (P=0.001), specifically neuroblastoma (P=0.002). Fever in the child group (P=0.02), was the most statistically significant presenting complaint related exclusively with lymphoid tumors.

Conclusions: Mediastinal mass epidemiological data vary according to populations; thus it is of utmost importance to acknowledge local patients' characteristics in order to narrow the clinical and pathological differential diagnosis.

Keywords: Mediastinal mass; neuroblastoma; posterior mediastinum; Colombia

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^ ORCID: 0000-0001-8274-6014.

Introduction

Mediastinal tumors are a heterogenous group of unrelated neoplasms that share the mediastinal anatomical location. Mediastinal masses are rare neoplasms which usually affect adults, with an estimated incidence in the adult general population of 0.01% (1). The mediastinum is the central portion of the thoracic cavity in which many vital organs reside such as the heart and large vessels. Traditionally, the mediastinum has been divided into three compartments, anterior, middle and posterior (2), with preferences of some histological tumor types for each compartment. Therefore, thymomas and lymphomas predominate in the anterior compartment, germ cell tumors (GCTs) are more frequent in the middle compartment, while neurogenic tumors are more frequent in the posterior compartment (3).

The incidence of benign and malignant tumors in children and adults has contradictory results depending on the case series and predominance of tumor location (4-6). Multicenter studies in different continents have shown different distribution patterns, mainly in terms of tumor types (7). There are no local publications regarding mediastinal masses, as such the clinical and pathological characteristics of this group of tumors in our population has been overlooked. With the aim of describing the clinicopathological characteristics of mediastinal masses in children and adults, a 13-year period [2010–2022], including only primary mediastinal tumors, was retrospectively reviewed. Upon comparison, some statistically significant results regarding tumor location, tumor type, histological type and presenting complaint were found, which run contrary to the results of surveys with similar objectives. We present this article in accordance with the STROBE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-25/rc).

Highlight box

Key findings

- The anterior mediastinal compartment was the most frequent location considering all tumors. Significant differences were present in adults' anterior compartment and child's posterior compartment for malignant tumors.

What is known and what is new?

- Different continents have shown different distribution patterns, mainly in terms of tumor types.
- To the best of our knowledge this is the first publication regarding mediastinal tumors in Medellín (Colombia).

What is the implication, and what should change now?

- Mediastinal mass epidemiological data vary according to populations; thus, it is of utmost importance to acknowledge local patients' characteristics to narrow the clinical and pathological differential diagnosis.

Methods

Ethics and cases acquisition

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Institutional Review Board of Hospital San Vicente Fundación (No. 082021). Individual consent for this retrospective analysis was waived. University of Antioquia is informed and agreed the study. All patients were Colombian, and residents of Antioquia (Colombia). After searching the Hospital San Vicente Fundación and University of Antioquia Pathology Department's database from 2010 to 2022 for mediastinal masses, 589 reports were retrieved. Then, reports with diagnoses of infections, metastatic disease, thyroid and pulmonary tumors were excluded, leaving 110 patients with primary mediastinal tumors. The anatomical location was extracted from radiology imaging reports such as computed tomography (CT), positron emission tomography-CT (PET-CT) and magnetic resonance imaging (MRI). Four anatomical locations of the neoplasms were differentiated, anterior mediastinum (prevascular), middle mediastinum (visceral), posterior mediastinum (paravertebral) and a "whole" category when the neoplasm occupied all the previously mentioned locations. The slides from the 110 primary mediastinal tumors were reviewed for diagnostic confirmation, and the medical charts were also reviewed for confirmation of demographic variables and identification of presenting complaint.

The 5th edition of the World Health Organization (WHO) Thoracic Tumours was use to establish a single coherent neoplasms classification (8). The 110 cases were divided based on age into two groups, children and adults. According to Colombian regulation a child is a right-holding subject from birth to 12 years old, and an adolescent is a right-holding subject from 12 to less than 18 years old. Therefore, both children and adolescents were included in the child group, while the adult group included patients of more than 18 years of age.

Statistical analysis

The two groups were compared, looking for statistically significant differences (P<0.05), by age, sex, tumor type, location, histological type, sex and presenting complaint. The two-proportions z-test (X-squared, two-sided, 95 percent confidence) in R software version 4.0.3 (2020-10-10) was used for statistical analysis.

Results

A total of 110 patients with primary mediastinal tumors were identified, 47 children and 63 adults. The mean age in the child group was 8 years and in the adult group 41.7 years (*Table 1*). In the child group, there were 30% (14/47) females and 70% (33/47) males, while in the adult group there were 46% (29/63) females and 54% (34/63) males. In both groups, most of the tumors were malignant, 81% (38/47) in the child group and 90% (57/63) in the adult group. There were non-significant statistical P values upon comparison of sex and tumor type between the groups.

There were 19 different presenting complaints in patients with primary mediastinal masses. The most frequent presenting complaint was dyspnea, chest pain, fever, cough and superior vena cava (SVC) syndrome. Mediastinal mass as an incidental finding was present in three patients, and 11 patients have unique presenting complaints in the study group (*Table 1*). Fever was the only presenting complaint with a significant statistical difference among children and adults (P=0.02), due to its high incidence in the child group.

Tumor type and location of mediastinal tumors

The most common location of mediastinal tumors in children and adults was the anterior mediastinum with an overall incidence of 61%, and a distribution of 49% (23/47) and 70% (44/63) respectively (*Table 2*). Upon comparison for all tumors, the anterior mediastinal location had a statistically significant difference in favor of the adult group (P=0.042).

The second most frequent location was the posterior compartment with an overall incidence of 25%, present in 40% (19/47) in the child group and 13% (8/63) in the adult group. Posterior location of tumors had significant differences in all tumors in favor of the child group (P=0.001), explained by the high incidence of tumors in this location in the child group, 19/47 cases, compared to just 8/63 cases in the adult group. Tumor incidence of 12% in the middle compartment and 2% in the whole mediastinal location represented a low proportion of cases. There were three tumors in which the anatomical location cannot be specified due to their large size and were thus interpreted as occupying the whole mediastinal compartment.

Most of the benign tumors in children were located in the mediastinal posterior compartment 56% (5/9), whereas adult benign tumors were mostly located in the posterior mediastinum 83% (5/6). Comparing malignant tumors between groups, malignant tumors were more frequent in the anterior mediastinum in both groups, 58% (22/38) in children and 79% (45/57) in adults. Statistically significant results regarding malignant tumors were related to posterior mediastinal location (P=0.001) in the child group, and the anterior location (P=0.02) in the adult group.

Profile of mediastinal tumors

The mediastinal compartment can harbor benign and malignant tumors like any other anatomical location. As previously stated, most of the pediatric mediastinal masses were malignant, and 66% were lymphoid tumors (25/38) (*Table 3*). Among lymphomas, T-cell lymphoblastic lymphoma was the most frequent hematolymphoid neoplasm present in 39% of the cases (15/38), a mean patient age of ten years, followed by B-cell lymphomas with 16% of the cases (6/38), and a mean patient age of 12 years. Hodgkin lymphoma corresponded to 11% of cases (4/38), with a mean patient age of eleven years. The second most frequent histological type of malignant neoplasm were neurally derived (29%), comprised of 21% (8/38) neuroblastomas with a mean patient age of 3 years, and 8% (3/38) ganglioneuroblastoma cases. Benign tumors were from several origins such as germ cells (3 benign cystic teratomas), neurally derived (one neurofibroma and one ganglioneuroma), and three benign cystic lesions of different epithelial linings.

Regarding adults, lymphoid neoplasms were also the most frequent malignant tumors, being present in 56% (32/57) of cases. Most of the mediastinal lymphomas were B-cell lymphomas 63% (20/32), with a mean patient age of 37.7 years, while Hodgkin lymphomas with 25% (8/32), a mean patient age of 27 years, and T-cell lymphomas with 13% (4/32) and a mean patient age of 35 years were the second and third in frequency respectively. The second most frequent malignant tumors in adults were thymic epithelial tumors representing 25% (14/57). Malignant GCTs represented 13% of cases (7/53), with a mean patient

Table 1 General characteristics of patients with primary mediastinal masses

Characteristics	Children (N=47)	Adults (N=63)	Total (N=110)	P value (children *vs.* adults)
Mean age (years)	8	41	49	
Sex				
Female	14 [30]	29 [46]	43	0.13
Male	33 [70]	34 [54]	67	0.13
Tumor type				
Benign	9 [19]	6 [10]	15	0.24
Malignant	38 [81]	57 [90]	95	0.24
Tumor type and sex				
Benign female	2 [4]	1 [2]	3	NS
Benign male	7 [15]	5 [8]	12	0.40
Malignant female	12 [26]	28 [44]	40	0.07
Malignant male	26 [55]	29 [46]	55	0.44
Presenting complaint				
Dyspnea	11 [23]	18 [29]	29	0.70
Chest pain	6 [13]	22 [35]	28	0.02
Cough	12 [26]	7 [11]	19	0.08
Fever	7 [15]	1 [2]	8	0.02
SVC syndrome	4 [9]	4 [6]	8	0.95
Incidental	2 [4]	1 [2]	3	0.80
Facial swelling	0	2 [3]	2	0.61
Precordial chest pain	0	2 [3]	2	0.61
Abdominal pain	0	1 [2]	1	>0.99
BOS	1 [2]	0	1	0.88
Dysphagia	1 [2]	0	1	0.88
Headache	1 [2]	0	1	0.88
Melena	0	1 [2]	1	>0.99
Myalgia	0	1 [2]	1	>0.99
Nausea	0	1 [2]	1	>0.99
Neck mass	1 [2]	0	1	0.88
Paraneoplastic syndrome	1 [2]	0	1	0.88
Ptosis	0	1 [2]	1	>0.99
Sternal mass	0	1 [2]	1	>0.99

Data are presented as number or n (%). SVC, superior vena cava; BOS, bronchial obstruction syndrome; NS, non-statistically significant.

Table 2 Primary mediastinal tumors by location and tumor type

Location	All tumors, n [%]				Bening, n [%]				Malignant, n [%]			
	Children (N=47)	Adults (N=63)	Total	P value	Children (N=9)	Adults (N=6)	Total	P value	Children (N=38)	Adults (N=57)	Total	P value
Anterior	23 [49]	44 [70]	67 [61]	0.042	1 [11]	0	1 [7]	>0.99	22 [58]	45 [79]	67 [70]	0.048
Middle	4 [9]	9 [14]	13 [12]	0.53	2 [22]	1 [17]	3 [20]	0.90	2 [6]	7 [12]	9 [9]	0.27
Posterior	19 [40]	8 [13]	27 [25]	0.001	5 [56]	5 [83]	10 [66]	0.38	14 [36]	3 [5]	17 [18]	0.001
Whole	1 [2]	2 [3]	3 [2]	>0.99	1 [11]	0	1 [7]	0.74	0	2 [4]	2 [3]	0.56

age of 26 years, with cases in the histological spectrum for this kind of neoplasm. There were two malignant, soft tissue tumors, one high grade fibrosarcoma and an undifferentiated pleomorphic sarcoma. followed by three neurally-derived tumors, two Schwannomas and one neurofibroma, and three benign cystic lesions. One patient with B-cell lymphoma was human immunodeficiency virus (HIV) positive.

For all tumors, most of the anteriorly located neoplasms in both groups were represented by lymphoid type tumors (45/110), and the significant difference in the anterior compartment (P=0.042) in favor of the adult group can be explained due to the exclusive location of thymic tumors in this anatomical site (*Table 4*). The same reason for anterior-exclusive thymic epithelial tumor location explained the significant difference (P=0.02) in malignant tumors in the anterior compartment of adults, because thymic tumors were only present in patients from this group (P=0.004).

Regarding posterior location, the significant differences in the child group (P=0.001), are due to the important presence of neurally-derived tumors in this compartment, specifically neuroblastomas (P=0.002) (*Table 4*) and ganglioneuroblastomas, considering there were no malignant, neurally-derived tumors in the adult group. Thymic tumors were exclusive to the adult group, as were poorly differentiated endocrine tumors and malignant soft tissue tumors. There were no malignant GCTs in the child group, and the predominant lymphoid tumors varied with significant statistically differences according to the group. T-cell lymphoblastic lymphomas had a higher incidence in the child group (P=0.001), and B-cell lymphomas in the adult group (P=0.04) and there was no statistically significant difference regarding Hodgkin lymphoma. The only statistically significant result when comparing the sexes was for male children with T-cell lymphoblastic lymphomas (P=0.01).

Presenting complaints

Despite their common location, the clinical symptoms of mediastinal tumors vary. We cannot find any concordance related to symptoms and anatomical locations (*Table 5*). Fever (P=0.02) and chest pain (P=0.02) were the symptoms presenting a statistically significant difference between children and adults. All the patients with fever as the presenting complaint had malignant tumors, specifically lymphoid tumors, located in the anterior (seven cases) and posterior compartment (one case). Chest pain was associated with adult tumors without any statistically significant differences in tumor type or anatomical location. Fever and cough were two ominous symptoms related to malignant type tumors in the clinical context of an anterior mediastinal mass in adults.

Discussion

In the analyzed mediastinal mass groups, we found some statistically significant differences, regarding tumor location, tumor type, histological type, sex and presenting complaint. Regarding location, the anterior mediastinal compartment was the most frequent location considering all tumors, with a significant difference (P=0.042) favoring the adult group. This difference was also present in malignant tumors (P=0.02), which can be explained in both situations by the exclusive incidence of thymic tumors in the adults' anterior compartment. In contrast, malignant tumors show a statistically significant difference (P=0.001) in the posterior compartment of the child group, associated with the high incidence of neurogenic tumors in this group (P=0.001), specifically neuroblastoma (P=0.002). Additionally, T-cell lymphoblastic lymphomas had a higher incidence in the child group (P=0.001), especially in males (P=0.01), and B-cell lymphomas in the adult group (P=0.04).

Table 3 Histological type of mediastinal masses in children and adults

Histological type	Children		Adult		P value
	Female	Male	Female	Male	
Thymic tumors	N=0		N=14		0.001
Thymomas	0	0	7	4	
Thymic carcinoma	0	0	1	2	
Germ cell tumors	N=3		N=7		NS
Teratoma	2	1	0	0	
Seminoma	0	0	0	2	
NSGCT	0	0	0	5	
Lymphoid tumors	N=25		N=32		0.01
T lymphoblastic lymphoma	3	12	2	2	
B lymphoma	3	3	8	12	
Hodgkin lymphoma	0	4	7	1	
Neurogenic tumors	N=13		N=3		0.001
Neuroblastoma	2	6	0	0	
Ganglioneuroblastoma	2	1	0	0	
Neurofibroma	0	1	0	1	
Ganglioneuroma	0	1	0	0	
Schwannoma	0	0	0	2	
Cyst	N=3		N=3		NS
Lymphangioma	0	1	0	1	
Bronchogenic cyst	0	1	1	0	
Enteric cyst	1	0	0	0	
Thymic cyst	0	0	0	1	
Soft tissue	N=3		N=2		NS
Lipoma	0	1	0	0	
Liposarcoma	1	0	0	0	
PNET	1	0	0	0	
Fibrosarcoma	0	0	1	0	
UPS	0	0	0	1	
PDN carcinoma	0	0	2	0	NS

NSGCT, nonseminomatous germ cell tumors; PNET, peripheral primitive neuroectodermal tumors; UPS, undifferentiated pleomorphic sarcoma; PDN, poorly differentiated neuroendocrine; NS, non-statistically significant.

Table 4 Comparison of histological type by location and age

Histological type	Children					Adults					P value
	Ant	Middle	Post	Whole	Total	Ant	Middle	Post	Whole	Total	
Thymic tumors											
Thymomas	–	–	–	–	–	11	–	–	–	11	0.004
Thymic carcinoma	–	–	–	–	–	3	–	–	–	3	NS
Germ cell tumors											
Teratoma	1	1	–	1	3	–	–	–	–	–	NS
Seminoma	–	–	–	–	–	1	–	–	1	2	NS
NSGCT	–	–	–	–	–	4	1	–	–	5	NS
Lymphoid tumors											
T lymphoblastic	15	–	–	–	15	4	–	–	–	4	0.001
B lymphoma	3	2	1	–	6	13	4	2	1	20	0.04
Hodgkin lymphoma	3	–	1	–	4	7	1	–	–	8	NS
Neurogenic tumors											
Neuroblastoma	–	–	8	–	8	–	–	–	–	–	0.002
Ganglioneuroblastoma	–	–	3	–	3	–	–	–	–	–	NS
Neurofibroma	–	1	–	–	1	–	–	1	–	1	NS
Ganglioneuroma	–	–	1	–	1	–	–	–	–	–	NS
Schwannoma	–	–	–	–	–	–	–	2	–	2	NS
Cyst											
Lymphangioma	–	–	1	–	1	–	–	1	–	1	NS
Bronchogenic cyst	–	–	1	–	1	–	1	–	–	1	NS
Enteric cyst	–	–	1	–	1	–	–	–	–	–	NS
Thymic cyst	–	–	–	–	–	–	–	1	–	1	NS
Soft tissue											
Lipoma	–	–	1	–	1	–	–	–	–	–	NS
Liposarcoma	1	–	–	–	1	–	–	–	–	–	NS
PNET	–	–	1	–	1	–	–	–	–	–	NS
Fibrosarcoma	–	–	–	–	–	1	–	–	–	1	NS
UPS	–	–	–	–	–	1	–	–	–	1	NS
PDN carcinoma	–	–	–	–	–	–	1	1	–	2	NS

Ant, anterior; Post, posterior; NSGCT, nonseminomatous germ cell tumors; PNET, peripheral primitive neuroectodermal tumors; UPS, undifferentiated pleomorphic sarcoma; PDN, poorly differentiated neuroendocrine; NS, non-statistically significant.

Table 5 Presenting complaints according to mediastinal location and age

Location	Presenting complaint	Benign		Malignant		Total
		Children (N=9)	Adults (N=6)	Children (N=38)	Adults (N=57)	
Anterior	Dyspnea	1	–	4	14	19
	Fever	–	–	6	1	7
	Cough	–	–	5	4	9
	Chest pain	–	–	3	14	17
	SVC syndrome	–	–	3	3	6
	Myalgias	–	–	–	1	1
	Precordial chest pain	–	–	–	2	2
	Facial swelling	–	–	–	2	2
	Melena	–	–	–	1	1
	Nausea	–	–	–	1	1
	Abdominal pain	–	–	–	1	1
	Neck mass	–	–	1	–	1
	Ptosis	–	–	–	1	1
Middle	Cough	1	–	–	2	3
	Dyspnea	1	–	1	1	3
	SVC syndrome	–	–	1	1	2
	Chest pain	–	1	–	3	4
Posterior	Dyspnea	–	–	4	2	6
	Chest pain	–	4	2	–	6
	Cough	3	–	3	1	7
	Fever	–	–	1	–	1
	BOS	1	–	–	–	1
	Headache	–	–	1	–	1
	Dysphagia	–	–	1	–	1
	Paraneoplastic syndrome	–	–	1	–	1
	Incidental	1	1	1	–	3
Whole	Dyspnea	1	–	–	–	1
	Chest pain	–	–	–	1	1
	Sternal mass	–	–	–	1	1

SVC, superior vena cava; BOS, bronchial obstruction syndrome.

Fever in the child group (P=0.02) was the most statistically significant presenting complaint related exclusively with lymphoid tumors. Symptomatology is related to size and/or compression or direct invasion of adjacent structures, that is why there is a wide spectrum of symptomatology associated with mediastinal masses (9,10). In the background review, we cannot find a specific symptomatology consistently associated with a histological type or mediastinal

compartment location.

Azarow and colleagues analyzed almost 40 years of mediastinal masses in a pediatric population (62 patients) and adults (195 patients) at a single center in the United States, finding a significantly increased incidence of lymphomas in adults (P<0.05) and neurogenic tumors in child (P<0.05), while there were no differences in thymic tumors (11). In our results, there were no differences in lymphoma incidence among the groups, thymic tumors were exclusively present in the adult population, whereas neurogenic tumors were also higher in the child group.

From Osaka (Japan), a 43-year mediastinal tumor review, found 106 children (with a cut off age of 15 years), and 522 adult patients. In this review, benign tumors were most frequent in both groups (66.9% in children and 53.1% in adults). The most frequent tumors in children and adults were neurogenic tumors (44.3%) and thymomas (36.2%) respectively, and regarding neurogenic tumors in children ganglioneuromas represented most of the tumors at 30% (12). Most of the tumors in the child and adult groups in our study were malignant, and most of them in both groups were lymphomas. Concerning neurogenic tumors in children, neuroblastoma had a statistically significant difference (P=0.002) among children and adults.

In another Japanese institution, Takeda and colleagues made a 49-year review of mediastinal tumors in 130 child and 676 adult patients (3). Takeda found in order of frequency in the adult group, 244 thymomas (36%), 106 GCTs (19%), 95 cysts (14%), and 82 lymphomas (12%). While in the child group, 60 neurogenic tumors (46%), 24 GCTs (19%), 17 lymphomas (13%), 10 congenital cysts (8%), and 5 thymomas (4%) were found. The most common location was the anterior compartment (68%) in adults and the posterior compartment (52%) in children. Contrary to these results, lymphoid tumors were the most frequent tumors in both groups of our study, we did not observe thymoma cases in the child group, and the anterior compartment was by far the most frequent location of tumors in both groups.

Regarding neurogenic tumors, age seems to be an important parameter increasing the odds of malignant behavior. In adults, neurogenic tumors are usually benign and represented by schwannomas and neurofibromas, with slight symptoms at presentation or discovered as an incidental finding (13). But in the case of children, neurogenic tumors are symptomatic (14), most of them are malignant and mostly neuroblastomas (15). In concordance with our results, neurogenic tumors were more frequent in the child group, most of them were malignant (P=0.001), and mostly neuroblastomas (P=0.002). Little is known about risk factors for developing neuroblastoma, and a huge variety of modifiable and non-modifiable conditions have been related, to date without clinical impact (16).

In our series, the most frequent malignant neoplasm in children and adults lacks clear risk factors. As expected, T-cell lymphoblastic lymphomas were most frequent in the child group and especially in males (17), and B-cell lymphomas were most frequent in adults (18). Risk factors for T-cell lymphoblastic lymphomas and mediastinal, diffuse B-cell lymphomas are mostly unknown, and so far, not related to virus (19,20). HIV positive patients have an increased risk for developing neoplasms, aggravating the natural history of the disease, especially those associated with Epstein-Barr chronic infection (21). However, most primary mediastinal lymphoid tumors are neither associated with any infectious agents nor Epstein-Barr virus, so there is no higher incidence of mediastinal masses in HIV patients. The latter, is a clear example of how a strong risk factor elsewhere, cannot influence an anatomical location like the mediastinum, if the most frequent tumors in this location have no association with that risk factor. There were not nuclear protein in testis (NUT) mutation associated midline carcinoma diagnosis.

Conclusions

In conclusion, mediastinal mass epidemiological data vary according to populations, thus it is of utmost importance to acknowledge local patients' characteristics in order to narrow the clinical and pathological differential diagnosis. Differences regarding histological type of tumors could be associated with population risk factor exposure in each geographical locale. Unfortunately, risk factors for most of the different types of mediastinal tumors are still unknown, therefore the unraveling of those possible risk factors could be an important field for further investigation.

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No artificial intelligence was used in the writing of the article or in the generation of the tables.

Footnote

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Original Article

Work-in-progress report: a prospective, multi-institutional observational study on intraoperative lymph node dissection for thymic epithelial malignancies with radiologically invasive features

Masatsugu Hamaji[1,2], Shigeto Nishikawa[2], Sho Koyasu[3], Yojiro Yutaka[2], Fumitsugu Kojima[4], Takao Nakanishi[5], Tomoya Kono[6], Yoshito Yamada[7], Kyoko Hijiya[8], Keiji Ohata[9], Ryutaro Kikuchi[9], Ei Miyamoto[10], Tatsuo Nakagawa[10], Mitsugu Omasa[5], Ryo Miyahara[6], Toru Bando[4], Hiroshi Date[2]

[1]Department of Thoracic and Cardiovascular Surgery, Nara Medical University, Kashihara, Japan; [2]Department of Thoracic Surgery, Kyoto University Hospital, Kyoto, Japan; [3]Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Hospital, Kyoto, Japan; [4]Department of Thoracic Surgery, St. Luke's International Hospital, Tokyo, Japan; [5]Department of Thoracic Surgery, Nishi Kobe Medical Center, Kobe, Japan; [6]Department of Thoracic Surgery, Kyoto City Hospital, Kyoto, Japan; [7]Department of Thoracic Surgery, Kyoto-Katsura Hospital, Kyoto, Japan; [8]Department of Thoracic Surgery, Shizuoka City Hospital, Shizuoka, Japan; [9]Department of Thoracic Surgery, Shiga General Hospital, Moriyama, Japan; [10]Department of Thoracic Surgery, Tenri Hospital, Tenri, Japan

Contributions: (I) Conception and design: All authors; (II) Administrative support: H Date; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Masatsugu Hamaji, MD, PhD. Department of Thoracic and Cardiovascular Surgery, Nara Medical University, 840 Shijo-Cho Kashihara, Nara, 634-8511, Japan; Department of Thoracic Surgery, Kyoto University Hospital, Kyoto, Japan. Email: mhamaji@kuhp.kyoto-u.ac.jp.

Background: Although lymph node metastasis may be an adverse prognostic factor for survival after resection of thymic epithelial malignancies, recommendations for intraoperative lymph node dissection (LND) lack consistency across various guidelines. This study aimed to investigate feasibility and characteristics of LND.

Methods: This is a work-in-progress report of our prospective, multi-institutional observational study to evaluate the feasibility and characteristics of LND in patients with resectable thymic epithelial malignancies that exhibit radiological invasive features such as size >5 cm, standardized uptake value >5, or suspected invasion of surrounding organs.

Results: In total, 25 patients were enrolled in this study. All patients underwent complete resection of the primary lesion with N1-level or N2-level LND. Among these, 22 (88%) patients underwent N1-level LND, and 20 (80%) patients underwent N2-level LND. No significant differences between the open and minimally invasive approaches were observed in the number of dissected stations (P=0.71), N1-level LND (P=0.49), or N2-level LND (P=0.69).

Conclusions: Intraoperative LND may be feasible in both approaches and may contribute to accurate nodal staging in resectable thymic malignancies with radiologically invasive features.

Keywords: Thymic carcinoma; thymoma; lymph node dissection (LND)

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Introduction

Recommendations for intraoperative lymph node dissection (LND) during the resection of thymic epithelial malignancies vary across the guidelines of the Japan Lung Cancer Society, the European Society of Medical Oncology, and the National Comprehensive Cancer Network (1-3). Recently, the International Thymic Malignancy Interest Group recommended routine systematic removal of lymph nodes (LNs) in both the anterior (N1-level) and deep (N2-level) regions (4) probably because previous retrospective studies suggested that LN metastasis may be an adverse prognostic factor for survival outcomes in patients undergoing resection of thymic epithelial malignancies (5-7). Thymic (neuroendocrine) carcinoma and/or a higher T stage, as recent studies suggested, are among the relevant factors associated with LN metastasis (8,9), and intraoperative LND plays an important role in nodal staging for thymic epithelial malignancies with those factors. However, the feasibility and characteristics of LND are largely unknown, likely because of the retrospective nature of these studies. Since a histological diagnosis is typically not available preoperatively for resectable thymic malignancies, we focused on the radiological invasive features that would be associated with thymic carcinoma or neuroendocrine carcinoma. This prospective observational study aimed to investigate the feasibility and characteristics of LND, including surgical approaches, detailed LN stations, and postoperative complications, in patients undergoing LND during resection of thymic epithelial malignancies with radiological invasive features. We present this article in accordance with the STROBE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-42/rc).

Highlight box

Key findings

- Intraoperative lymph node dissection (LND) may be feasible in both open approach and minimally invasive approach and both in N1-level and N2-level lymph nodes (LNs).

What is known and what is new?

- LN metastasis may be an adverse prognostic factor for survival after resection of thymic epithelial malignancies.
- In this study, 22 (88%) patients underwent N1-level LND, and 20 (80%) patients underwent N2-level LND. Stations 3a, 5, and 6 appeared to be the most frequently dissected among all the stations.

What is the implication, and what should change now?

- Intraoperative LND may contribute to accurate nodal staging in resectable thymic malignancies with radiologically invasive features.

Methods

This prospective, multi-institutional, observational cohort study was initiated in June 2021 at Kyoto University Hospital, Nara Medical University, Nishi Kobe Medical Center, Shiga General Hospital, Kyoto City Hospital, Tenri Hospital, Shizuoka City Shizuoka Hospital, Osaka Red Cross Hospital, Nagara Medical Center, Otsu Red Cross Hospital, St. Luke's International Hospital, and Kyoto-Katsura Hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved on June 21, 2021 by the Institutional Review Board of Kyoto University Hospital (reference number: R2996). Written informed consent was obtained from all the patients. All participating institutions were informed and agreed to the study. The number of dissected stations and the extent of LND were determined at the discretion of attending surgeons. Patients undergoing therapeutic resection for thymic epithelial malignancies >5 cm on preoperative computed tomography, whose standardized uptake value max on positron emission tomography was >5, or who were suspected of invading surrounding organs such as the lung, pericardium, heart, or great vessels were included. Patients who underwent surgical biopsy only and those diagnosed with malignancies other than thymic epithelial malignancies on final pathology were excluded. The recently introduced nodal map of the International Thymic Malignancy Interest Group/International Association for the Study of Lung Cancer and the Tumor, Node, Metastasis stage classification was used to group and stage the LNs (4).

Statistical analysis

Descriptive statistics for categorical variables are reported as frequencies and percentages, whereas continuous variables are reported as medians (ranges), as appropriate. The proportions of patients who underwent N1-level and N2-level LND were compared between the open and minimally invasive approaches using the Chi-square test. The number of dissected LN stations was compared between the open and minimally invasive approaches using the Mann-Whitney *U* test. All analyses were performed using JMP®

14 and SAS@ 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 25 patients were enrolled in this study. The background and characteristics of the enrolled patients were summarized in *Table 1*. The median size was 5.7 cm on preoperative computed tomography and the median standardized uptake value max was 5.13 on positron emission tomography. All patients underwent complete resection of the primary lesion along with LND. Grade 3 postoperative complication was noted in 4 patients (16%). The final pathology was thymoma in 18 (72%) patients and thymic carcinoma in 7 (28%) patients. Twenty-two (88%) patients had N1-level LNs evaluated and 20 (80%) patients had N2-level LNs evaluated among all patients. The median number of dissected LN stations was 2. Frequencies of LND in each station were shown for all patients in *Figure 1*, which suggested that stations 3a, 5, and 6 appeared to be the most frequently dissected among all the stations. *Figure 2* showed that frequencies of LND in each station in in open approach and minimally invasive approach. In *Figure 3*, frequencies of N1-level and N2-level LND were compared between open approach and minimally invasive approach, which resulted in no significant differences in N1-level LND (P=0.49), or N2-level LND (P=0.69). In *Figure 4*, the number of dissected stations was compared between open approach and minimally invasive approach, which resulted in no significant differences (P=0.71).

Discussion

Intraoperative LND during the resection of thymic epithelial malignancies are recommended by the guidelines from the Japan Lung Cancer Society, the European Society of Medical Oncology, and the National Comprehensive Cancer Network Guidelines, indications or details of LND were not specified (1-3).

Our previous study showed that preoperative radiological investigations appear to play a limited role in detecting

Table 1 The background and characteristics of the enrolled patients

Variables	All patients (n=25)	Open approach (n=12)	Minimally invasive approach (n=13)	P value
Age, years	56 [37–75]	51.5 [48–72]	62 [37–75]	0.24
Gender				0.16
Male	14	5 (41.7)	9	
Female	11	7 (58.3)	4	
Charlson comorbidity index	0 [0–2]	0 [0–2]	0 [0–2]	0.67
Size of primary lesions on CT, cm	5.7 [1.8–13.6]	6 [3.9–7.5]	5.7 [1.8–13.6]	0.28
SUVmax of primary lesions on PET	5.13 [2.2–16.1]	5.3 [2.2–13.2]	5.04 [2.2–16.1]	0.87
Any bulky (>1 cm in short-axis) or FDG-avid lymph node	2 (8.0)	1 (8.3)	1 (7.7)	0.95
Any preoperative treatment	2 (8.0)	2 (16.6)	0	0.22
Preoperative chemotherapy	1 (4.0)	1 (8.3)	0	
Preoperative chemoradiotherapy	1 (4.0)	1 (8.3)	0	
Completeness of resection	25 (100.0)	12 (100.0)	13 (100.0)	>0.99
Detailed surgical approach				
Median sternotomy		5 (41.7)	–	
Sternotomy and thoracotomy		6 (50.0)	–	
Transmanubrial		1 (8.3)	–	

Table 1 *(continued)*

Table 1 *(continued)*

Variables	All patients (n=25)	Open approach (n=12)	Minimally invasive approach (n=13)	P value
RATS		–	12 (92.3)	
Bilateral		–	6	
Unilateral		–	5	
Subxiphoid		–	1	
Unilateral VATS		–	1 (7.7)	
Any combined resection	12 (48.0)	9 (75.0)	3 (25)	0.009
Combined resected organs				
Lung	10 (40.0)	7 (58.3)	3 (23.1)	
Pericardium	7 (28.0)	6 (50.0)	1 (7.7)	
Left innominate vein	6 (24.0)	5 (41.7)	1 (7.7)	
Phrenic nerve	4 (16.0)	4 (33.3)	0	
Superior vena cava	1 (4.0)	1 (8.3)	0	
Operative time, minutes	272.5 [104–576]	310.5 [104–576]	226 [127–560]	0.28
Chest tube duration, days	3 [1–43]	4 [1–43]	3 [1–11]	0.10
Postoperative hospital stay, days	8 [3–55]	11 [7–55]	6 [3–41]	0.006
Perioperative transfusion	3 (12.0)	2 (16.6)	1 (7.7)	0.59
Any grade 3 or greater postoperative complication	4 (16.0)	2 (16.6)	2 (15.4)	0.93
Chylothorax	2 (8.0)	1 (8.3)	1 (7.7)	
Bilateral pleural effusion	2 (8.0)	1 (8.3)	1 (7.7)	
Final pathology				0.03
Type A thymoma	2 (8.0)	0	2 (15.4)	
Type AB thymoma	5 (20.0)	0	5 (38.5)	
Type B1 thymoma	3 (12.0)	1 (8.3)	2 (15.4)	
Type B2 thymoma	5 (25.0)	4 (33.3)	1 (7.7)	
Type B3 thymoma	3 (12.0)	3 (25.0)	0	
Squamous cell carcinoma	7 (28.0)	4 (33.3)	3 (23.1)	
Size of primary lesion specimens, cm	5.6 [0–9]	6 [0–9]	5 [1.9–7.5]	0.22
Final pathological TNM stage				0.27
ypT0N0M0	1 (4.0)	1 (8.3)	0	
T1N0M0	14 (56.0)	4 (33.3)	10 (76.9)	
T2N0M0	2 (8.0)	1 (8.3)	1 (7.7)	
T3N0M0	6 (24.0)	4 (33.3)	2 (15.4)	
T2N1M0	1 (4.0)	1 (8.3)	0	
ypT3N0M1	1 (4.0)	1 (8.3)	0	

Data are presented as median [range] or n (%). CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; RATS, robotic-assisted thoracoscopic surgery; SUV, standardized uptake value; VATS, video-assisted thoracoscopic surgery.

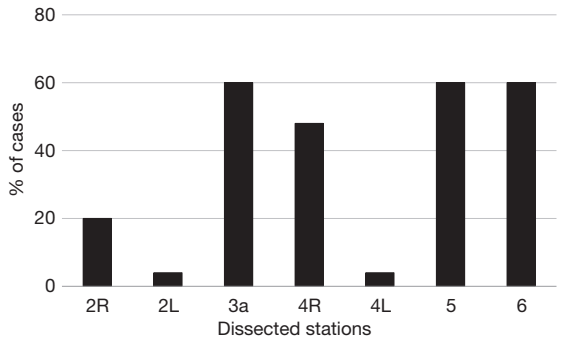

Figure 1 Frequencies of lymph node dissection in each station were shown in all patients.

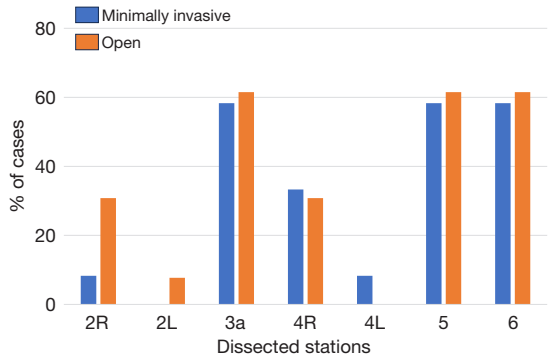

Figure 2 Frequencies of lymph node dissection in each station were shown in open approach and minimally invasive approach.

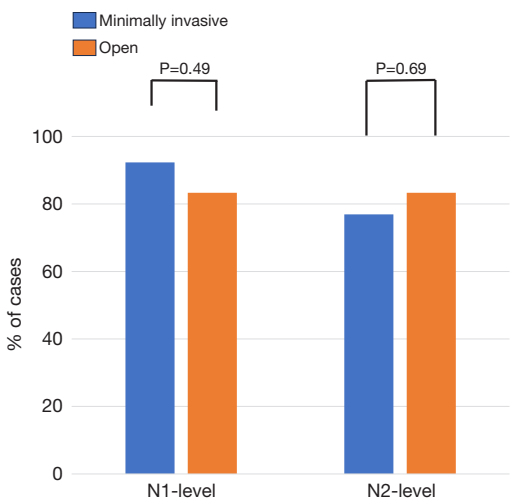

Figure 3 Frequencies of N1-level and N2-level lymph node dissection were compared between open approach and minimally invasive approach.

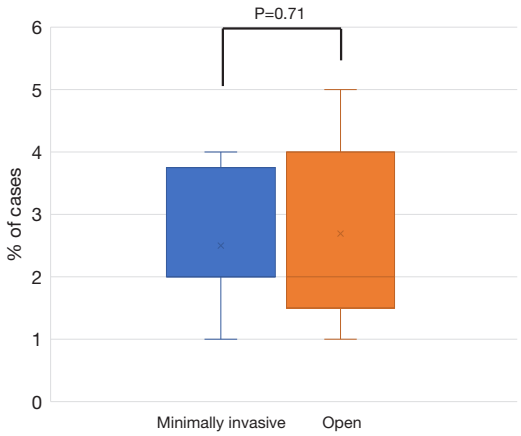

Figure 4 The number of dissected stations was compared between open approach and minimally invasive approach.

pathological LN metastases (10), therefore, in this study, we focused on radiological invasive features of the primary lesions.

The major findings of this work-in-progress report were that both N1-level and N-2 level LND were feasible both in open approach and minimally invasive approach and that intraoperative LND would contribute to nodal staging. It is challenging to estimate the time required for the LND, however, presumably it would be less than ten minutes because the procedure was performed in the same approach. We speculate that none of the postoperative complications were specifically attributed to LND, whereas we cannot completely deny that chylothorax was not associated with LND.

Of interest, *Figure 3* suggested that open approach appeared to have an advantage of a slightly more comprehensive access to N2-level LNs over minimally invasive approach, therefore, LND via open approach may be preferred in thymic carcinoma and/or higher T stage, which recent studies suggested as independent factors associated with LN metastasis (8,9). Because histological information is frequently unavailable preoperatively in resectable thymic malignancies, we added greater than 5 of standardized uptake value max on positron emission tomography as one of criteria for enrollment in this study, given the fact that a higher standardized uptake value may be associated with thymic carcinoma (11).

The limitations of our study included its observational design and the small number of patients. Owing to the small sample size (with a small number of patients from

each institution) and the only one case with LN metastasis, we were unable to perform multivariable analyses of factors associated with LN metastasis. The low positive rate (4%) in our preliminary data would be presumably due to the small sample size, which suggests it is too early to conclude that LND is not required in our cohort. The procedure of LND was not performed in a standardized manner, which should be investigated in a next study. Our patients were limited to surgical patients, and it remains unknown whether our findings can be applied to more advanced diseases or metastatic diseases.

Despite the above limitations, this work-in-progress report appears to contribute to current literature regarding LND during resection of thymic epithelial malignancies. We will continue to enroll eligible patients in this study in order to investigate any potentially relevant factors, other than tumor size and being FDG-avid, associated with LN metastasis.

Conclusions

In this work-in-progress report, we conclude that intraoperative LND may be feasible in both approaches and in resectable thymic malignancies with radiological invasive features.

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None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-24-42/rc

Data Sharing Statement: Available at https://med.amegroups.com/article/view/10.21037/med-24-42/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Kyoto University Hospital Institutional Review Board (reference number: R2996) and written consent was obtained from each patient. All participating institutions were informed and agreed to the study.

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Review Article

Hidden in plain sight: unknown anatomy depiction and applications of the aorto-esophageal ligament

Nanditha Guruvaiah Sridhara[1]^, Namratha Guruvaiah Sridhara[2]^, Janardhana Ponnatapura[3]^

[1]Department of Radiology, Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA; [2]School of Medicine, St. George's University, True Blue, St. George, Grenada; [3]Department of Cardiothoracic Radiology, Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA

Contributions: (I) Conception and design: Nanditha Guruvaiah Sridhara, J Ponnatapura; (II) Administrative support: J Ponnatapura; (III) Provision of study materials or patients: J Ponnatapura; (IV) Collection and assembly of data: Nanditha Guruvaiah Sridhara, Namratha Guruvaiah Sridhara; (V) Data analysis and interpretation: Nanditha Guruvaiah Sridhara, Namratha Guruvaiah Sridhara; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Janardhana Ponnatapura, MD. Department of Cardiothoracic Radiology, Wake Forest University Baptist Medical Center, 1 Medical Center Blvd., Winston-Salem, NC 27157, USA. Email: jponnata@wakehealth.edu.

Abstract: While it is not uncommon to see central mediastinal diseases on cross-sectional imaging, it is important to understand the pathway influencing the spread of disease at a radiological point of view. The advent of minimally invasive thoracic surgeries has led to the discovery of unknown tissue planes in the mediastinum such as the aorto-esophageal (AE) and aorto-pleural (AP) ligaments. In particular, the AE ligament is a portion of the mediastinal visceral fascia, which courses from the anterior aspect of the aorta to the left lateral aspect of the esophagus. It can be visualized on computed tomography (CT) and magnetic resonance imaging (MRI); it courses longitudinally from the level of the aortic arch to the level of the diaphragm. This recently discovered unknown anatomy aids us in understanding the possible pathway of spread of disease processes such as air, fluid, and soft tissue in the mediastinum. In addition, it acts as an important anatomical landmark in determining the location of lymph node metastases from esophageal cancer, which will further influence the possibility of thoracic duct resection/sparing. Finally, the AE ligament can be utilized in the preoperative planning of minimally invasive thoracic surgeries and can potentially be used as a dissection plane during esophagectomies.

Keywords: Aorto-esophageal ligament (AE ligament); mediastinum; esophageal cancer; surgical planning

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Introduction

The mediastinum was initially classified based on the lateral chest radiograph, but a newer system of classification developed by the International Thymic Malignancy Interest Research Group (ITMIG) has been accepted as the standard (1). This new schematic is based on cross-sectional imaging primarily computed tomography (CT) and divides the mediastinum into prevascular, visceral and paravertebral compartments (1). A unanimous system for classification of mediastinal compartments is necessary for various reasons including generating differential diagnoses for mediastinal diseases, planning surgical management and for ease of interaction with other clinicians (1). The advent of minimally invasive thoracic surgeries allowed for visualization of previously unknown tissue planes in the mediastinum such as the aorto-esophageal (AE) and aorto-

^ ORCID: Nanditha Guruvaiah Sridhara, 0000-0002-1103-9782; Namratha Guruvaiah Sridhara, 0009-0003-2102-049X; Janardhana Ponnatapura, 0000-0002-7459-0854.

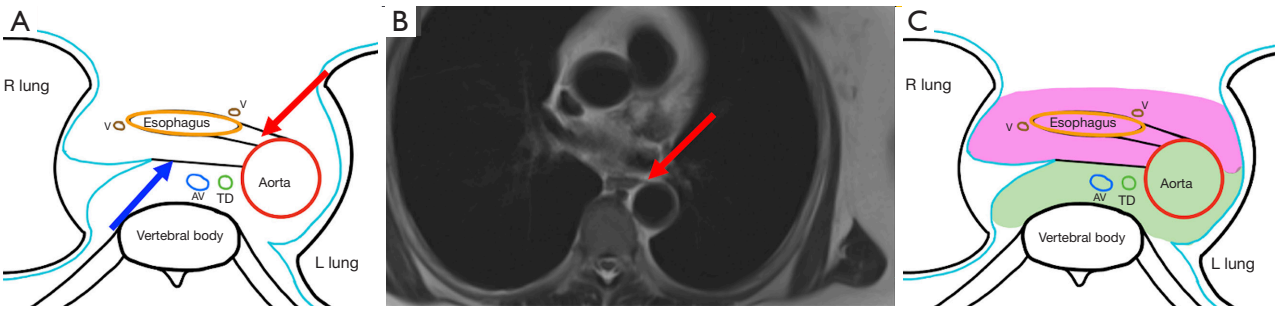

Figure 1 Anatomy of the AE ligament. (A) Schematic depicting the AE ligament (red arrow) and AP ligament (blue arrow) at the level between the tracheal bifurcation and the diaphragm. (B) Axial T2 weighted MRI depicting AE ligament (red arrow). (C) Division of posterior mediastinum by the AE ligament into anterior peri-esophageal space (pink) and posterior para-aortic (green) space. AE, aorto-esophageal; AP, aorto-pleural; AV, azygous vein; E, esophagus; MRI, magnetic resonance imaging; TD, thoracic duct; V, vagus nerve.

pleural ligament (AP) ligaments which were confirmed by Cuesta *et al.* through histological study (2). Furthermore, a study done by Weijs *et al.* identified these structures on T2 weighted magnetic resonance imaging (MRI) through an *ex-vivo* cadaveric study and *in-vivo* study involving patients with esophageal cancer (3). Our article focuses on depicting the anatomy of the AE ligament and its applications.

While analyzing central mediastinal diseases on cross-sectional imaging, it is important to understand the pathway influencing the spread of disease at a radiological point of view. In addition to depicting the anatomy, this article will also discuss the various applications of the AE ligament such as its role in influencing the restriction or spread of disease in the mediastinum, acting as an anatomic landmark in determining the location of lymph node metastases from esophageal cancer, which will further influence the possibility of thoracic duct resection/sparing; and its role in preoperative planning of minimally invasive thoracic surgeries/potential use as a dissection plane during esophagectomy.

Anatomy of the AE ligament

The AE ligament is a portion of the mediastinal visceral fascia, which courses from the anterior aspect of the descending thoracic aorta (11 o'clock position) to the left lateral aspect of the esophagus (two o'clock position) (*Figure 1A*). The AE ligament consists of two connective tissue layers with blood vessels and nerves coursing in between similar to mesentery however in contrast it is not lined with mesothelial cells (3). The AE ligament can be identified on cross-sectional imaging such as CT but is best visualized on T2 weighted MRI (*Figure 1B*). The course of the ligament starts at the level of the aortic arch and extends till the level above the diaphragm (3). However, in Weijs *et al.*'s study, the most common location where it was visualized by radiologists was in the para-aortic region at the T8–T10 level (3). The AE ligament divides the posterior mediastinum into an anterior 'peri-esophageal compartment' compartment containing the esophagus, vagus nerve, and carinal lymph nodes and a posterior 'para-aortic compartment', containing the thoracic duct, azygos vein, and occasionally lymph nodes (*Figure 1C*).

Role of imaging

In order to confirm the presence of the AE ligament; Weijs *et al.* [2017] conducted a two-arm study. The first arm involved an *ex-vivo* study where Transverse T2 weighted images of the thoracic region of one cadaver was taken using a 3 Tesla MRI. These images were taken within 24 hours post-mortem to avoid tissue decay/long term fixation (3). On the other hand, the second arm involved an *in-vivo* study where pre-treatment MRI of 34 patients with esophageal cancer was analyzed (3). These images were independently assessed by two radiologists for their presence and location and the results showed an inter-observer agreement was k value of 0.57 which showed substantial agreement (3).

Applications of the AE ligament

Spread of disease in the mediastinum

When assessing mediastinal diseases; whether it be gas, fluid or soft tissue masses on cross-sectional imaging, it is vital to pay attention to the factors that influence the restriction or

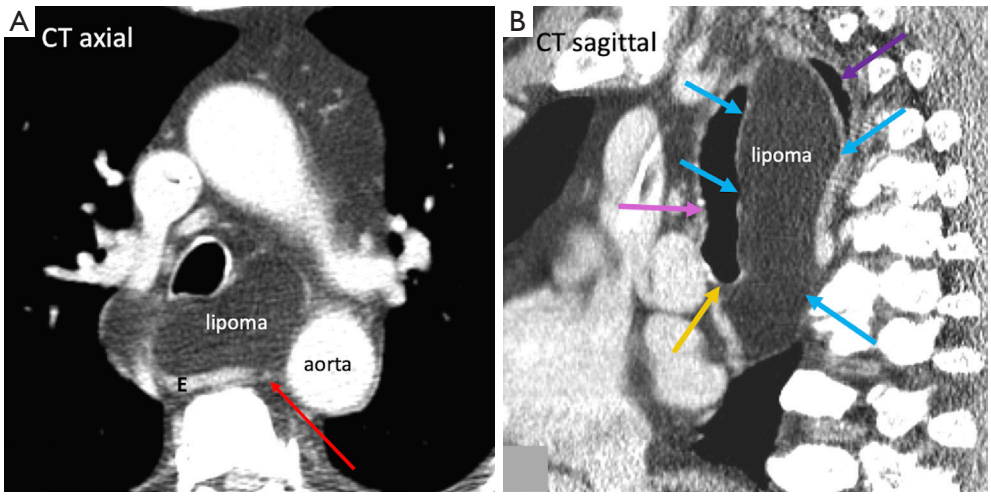

Figure 2 A 65-year-old male patient with mediastinal lipoma. (A) Axial contrast-enhanced chest CT image shows lipoma being limited axially by aorto-esophageal ligament (red arrow), E: esophagus. (B) Sagittal CT chest image shows lipoma (blue arrows) extending along the peri-esophageal space, displacing the trachea (pink arrow) and esophagus (purple arrow). Lipoma continues longitudinally below carina (orange arrow). CT, computed tomography.

spread of disease. Some pathologies that manifest as fluid in the mediastinum include fluid from esophageal perforation, hemorrhage from aneurysm rupture, infection originating from the deep neck or the abdomen etc. (4). On the other hand, some common etiologies for soft tissue disease in the mediastinum include fat lesions like lipoma, soft tissue lesions like thyroid masses/cysts, lymphadenopathy and primary/metastatic tumors (4). Finally, gas can manifest in the mediastinum from various sources such as visceral perforation, trauma, foreign bodies, excessive coughing/vomiting/retching, soft tissue infection etc. (4). The AE ligament plays a vital role in delineating the spread of these disease processes in the mediastinum. It serves as an axial barrier to soft tissue disease spread, while directing its spread along a longitudinal pathway (4). Thus, it inhibits the spread of soft-tissue disease in an antero-posterior direction depending on where the mass is located in relation to the AE ligament (*Figure 2*). However, fluid and gas have the potential to pass through the ligament (*Figure 3*).

Oncology imaging

AE ligament plays a key role during pre-op imaging for esophageal cancer, which is known for its frequent lymph node metastases and tumor ingrowth to the surrounding structures. Esophageal cancer is the eighth most common type of cancer and is the sixth leading cause of cancer death, with up to 0.54 million deaths worldwide in 2020 (5). The most common locations for esophageal cancer metastases are liver, lymph nodes, lung, bone and brain (5). Lymphatic spread is an important prognostic factor for esophageal cancer and standard treatment consists of neoadjuvant chemoradiation and trans-thoracic esophagectomy (TTE) with lymph node (LN) resection (6). Thoracic duct lymph nodes (TDLN) are found along the thoracic duct and are located posterior to the AE ligament in the para-aortic space (7). They are situated in the adipose tissue in between the thoracic esophagus and the descending aorta (7). TDLN metastases occur in highly advanced stages of esophageal cancer and survival in patients with TDLN metastases is identical to those with distant metastases (7). Thus, it is important to know the presence of TDLN metastases as it indicates a strong negative prognostic factor and lymphadenectomy of the TDLN with thoracic duct resection should be considered (7).

With the guide of pre-operative MRI, the AE ligament acts as an anatomical landmark to determine the location of the lymph node metastases and tumor ingrowth. As mentioned above the AE ligament divides the posterior mediastinum into an anterior 'peri-esophageal compartment' and posterior 'para-aortic compartment'. If there are lymph node metastases anterior to the AE ligament (peri-esophageal space), this may influence surgeons to perform less extensive resections possibly sparing the

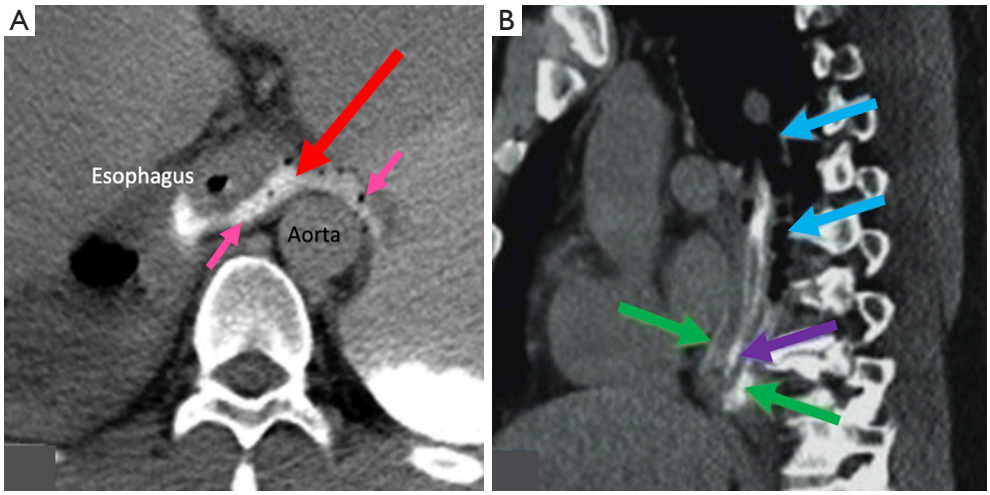

Figure 3 A 54-year-old male patient with distal esophageal perforation. (A) CT axial chest shows oral contrast and air (pink arrows) due to esophageal perforation passing through the AE ligament (red arrow). (B) CT sagittal chest image shows contrast material (green arrows) and air (blue arrows) in the periesophageal space and esophageal lumen (purple arrow). AE, aorto-esophageal; CT, computed tomography.

para-aortic space and its contents; especially avoiding the complications that come with TD resection (8). However, if there are metastases to the TDLN; which are located posterior to the AE ligament (para-aortic space), treatment will require esophagectomy with resection of the thoracic duct and TDLN (7). Some of the benefits of this surgical plan is that it will lead to increased lymph node yield, increased radicality of surgical resection, as the adipose tissue surrounding the TD and esophagus that could contain cancer cells can be removed simultaneously; and increased circumferential resection margin (CRM) (7). Transthoracic minimally invasive esophagectomy (TMIE) including thoracic duct resection was associated with improved recurrence free survival (RFS) (7). On the other hand, the complications of thoracic duct resection include postoperative leak and resultant chylothorax, edema due to the interruption of lymph flow or piling of lymphatic fluid, malabsorption and acute pancreatitis secondary to resection, negative effect on early postoperative nutrition (9). All in all, the AE ligament acts as an important landmark in determining the location of lymph node metastases from esophageal cancer and can aid in choosing the proper surgical management.

Pre-operative planning

Good regional anatomical knowledge is essential especially during minimally invasive thoracic surgeries as it requires working in a confined space with many important structures. Surgeons need to be aware that tissues such as the AE ligament exist and that it can be used as a landmark to differentiate the beginning and end of the peri-esophageal and para-aortic space and its contents (8). In addition, connective tissue layers are frequently used as dissection planes during operation in other regions, such as 'the white line of Toldt' (in the mesocolon) or 'the holy plane of Heald' (the mesorectum); which has been instrumental in achieving complete resections for rectal cancer (3). Similarly, the AE ligament can potentially be used as a dissection plane during esophagectomies (8).

Conclusions

AE ligament is a recently discovered portion of the mediastinal visceral fascia, which courses horizontally from the anterior aspect of the aorta to the left lateral aspect of the esophagus. It can be visualized on cross-sectional imaging such as CT and MRI from the level of the aortic arch to the level of the diaphragm. Some of its applications include acting as an axial barrier to the spread of soft tissue disease in the mediastinum, while allowing gas and fluid to pass through. It also acts as an important anatomical landmark in determining the location of esophageal cancer lymph node metastases, which will further influence the possibility of thoracic duct resection/sparing. Finally, it is vital in preoperative planning of minimally invasive thoracic surgeries and can potentially be used as a dissection plane

during esophagectomy. Although the AE ligament seems like an inconspicuous feature in the grand scheme of the mediastinum, it plays a pivotal role. We believe that this novel topic has potential for further research into its applications.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The patients have given consent and their identities have been protected. Ethics approval was not required by our institution for the purposes of this review article.

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Review Article

Endoscopic management of tracheoesophageal fistulas: a narrative review

Michal Senitko[1,2], Meredith Sloan[1], Yanglin Guo[1]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Mississippi Medical Center, Jackson, MS, USA; [2]Division of Cardiothoracic Surgery, University of Mississippi Medical Center, Jackson, MS, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Michal Senitko, MD. Division of Pulmonary, Critical Care, and Sleep Medicine, University of Mississippi Medical Center, 2500 N. State St., Jackson, MS 29216, USA; Division of Cardiothoracic Surgery, University of Mississippi Medical Center, Jackson, MS, USA. Email: msenitko@umc.edu.

Background and Objective: The formation of pathologic communication between respiratory and digestive tracts is a morbid condition which possesses management challenges regardless of its etiology. Severity of the symptoms related to contamination of the respiratory tract with oral and gastric secretions calls for timely seal and closure translating into improved mortality. The aim of this article is to review the latest data in regards of tracheoesophageal fistulas (TEFs) and the endoscopic methods of their management.

Methods: A literature review was conducted in the National Institute of Health's PubMed database in July 2024. Only studies published in English with abstracts available were included. Over 2,700 articles were found. The first 800 abstracts for "tracheoesophageal fistula" were reviewed and used to guide more detailed searches. Fifty-seven publications were considered relevant, and their full text studied to collate information for this review.

Key Content and Findings: We summarized the endoscopic approaches to management of both benign and malignancy associated TEFs as reported in the literature to this date. Despite several new non-operative approaches, esophageal stenting with or without airway stenting remains the mainstem of the endoscopic treatment of the fistulas. Self-expanding metallic stents are the mainstay of this approach. Esophageal stenting in particular has been associated with improved fistula closure and quality of life, as well as possible improvement in mortality for malignancy associated fistulas. More novel methods such as suturing or clips, occluding devices, and tissue adhesives also show promise. The quality control after the initial endoscopic management sets the future steps. Early multidisciplinary discussion among aerodigestive specialists including endoscopists and surgeons with involvement of palliative care team is strongly recommended.

Conclusions: The ever-evolving landscape of endoscopic therapies offers minimally invasive approach to TEFs especially for patients with prohibitive conditions to surgery or for patients needing a temporizing measure until the definitive surgical treatment is possible.

Keywords: Tracheoesophageal fistula (TEF); esophagorespiratory fistula; aerodigestive fistula; esophageal stenting; airway stenting

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Introduction

Background

Tracheoesophageal fistulas (TEFs) are abnormal connections between the esophagus and airway that result in gastric contents spilling into the airway. The clinical effect of this complication can severely impact quality of life with symptoms including, coughing, dysphagia, hemoptysis or hematemesis, recurrent aspiration and pneumonia, and hospitalization for respiratory failure. Conservative management often includes the recommendation to stop oral intake, leading to further decline in quality of life. This makes alternatives in management an important consideration (1).

In adults, TEFs are usually an acquired condition, and are classically divided into benign and malignant etiologies. Acquired benign fistulas account for approximately 50% of all acquired fistulas (2). Benign fistulas are still a morbid condition as they are complicated by recurrent aspiration and rarely close spontaneously; however, they carry a better prognosis with more definitive surgical options available compared to fistulas associated with malignancy. Etiologies for benign fistulas are often iatrogenic, the most common of which include post-intubation injury, post-radiation, and post-surgical (such as esophagectomy or laryngectomy). Post-intubation injury accounts for 75% of all acquired benign TEFs (3). Other causes include traumatic injuries, foreign bodies, invasive infections such as invasive candidiasis (4), and late presenting congenital fistulas. Successful closure of TEF is achieved with several surgical techniques in order to repair and restore normal breathing and swallowing. Surgical approaches generally include primary esophageal or tracheal closure or tracheal and esophageal resection and reconstruction. All approaches typically include interposing pedicled muscle or omental flaps (5).

Fistulas associated with malignancy carry a poor prognosis. They most commonly arise from esophageal cancer, comprising about 77% of cases. Tracheal and lung cancers make up much of the remainder (1). TEFs can occur in 5–15% of untreated esophageal cancer cases with further progression after treatment with radiation and/or chemotherapy. The development of fistulas is more uncommon in lung cancer, occurring less than 1% of the time. Left untreated, sepsis from aspiration is inevitable and often fatal. Overall prognosis of these patients is very poor with less than a year at the diagnosis of a TEF (6). Surgical approaches carry high complication rate (40%) and mortality (14%) (7). The recent focus has been therefore on less invasive treatment approaches. There is emerging evidence that treatment of TEF can improve survival (8), which makes an understanding of the available treatment options of even more importance beyond just a palliation of symptoms.

Rationale and knowledge gap

With the ever-evolving landscape of endoscopic therapies, more patients opt for less invasive treatment options for TEFs, especially if any prohibitive conditions for surgery are present. Esophageal self-expanding metallic (SEM) stents have been the mainstay and most reported of the non-surgical options. However, more novel approaches have been increasingly reported. As the response to therapy influences prognosis, a review of the available options and outcomes allows physicians to provide the best options for their patients. There are many developing therapies that use already commercially available products that endoscopists may be able to use in the appropriate clinical settings.

Objective

This article aims to summarize the endoscopic approaches to management of both benign and malignancy related TEFs as reported in the literature. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-45/rc).

Methods

A literature review was conducted in the National Institute of Health's PubMed database in July 2024. The search strategy is summarized in the *Table 1*. Only studies published in English with abstracts available were included. Over 2,700 articles were found. The first 800 abstracts returned for "tracheoesophageal fistula" were reviewed and used to guide more detailed searches including: ("tracheoesophageal fistula" AND stent), ("tracheoesophageal fistula" AND suture), ("tracheoesophageal fistula" AND occlude*), ("tracheoesophageal fistula" AND atrial), ("tracheoesophageal fistula" AND ventricular), ("tracheoesophageal fistula" AND glue), ("tracheoesophageal fistula" AND fibrin), ("tracheoesophageal fistula" AND histoacryl), ("tracheoesophageal fistula" AND cyanoacryl),

Table 1 The search strategy summary

Items	Specification
Date of search	July 2024
Databases searched	National Institute of Health's PubMed
Search terms used	Initial search: tracheoesophageal fistula
	Subsequent specific searches: tracheoesophageal fistula AND stent, AND suture, AND occlude*, AND atrial, AND ventricular, AND glue, AND fibrin, AND histoacryl, AND cyanoacryl, AND alcohol, AND bioposthe*, AND tissue, AND matrix, AND platelet
Timeframe	April 1993 to January 2024
Inclusion criteria for the searches	Articles in English language
	Articles with an abstract
Selection process	First 800 abstracts were reviewed independently by M.E.S.
	Specific searches for TEF and different endoscopic methods were performed by Meredith Sloan and Michal Senitko
	Prospective and retrospective studies, case series, and case reports were selected by Michal Senitko and included in the *Table 2*

TEF, tracheoesophageal fistula.

("tracheoesophageal fistula" AND alcohol), ("tracheoesophageal fistula" AND bioprosthe*), ("tracheoesophageal fistula" AND tissue), ("tracheoesophageal fistula" AND matrix), and ("tracheoesophageal fistula" AND platelet). References from returned articles were also reviewed for additional relevant publications. Total of 57 publications were considered relevant, and their full text was studied to collate information for this review. Thirty-four of those, in the format of scientific studies, case series, and case reports are summarized in *Table 2*.

Endoscopic management of TEFs

General considerations

Patients with either malignant or benign fistulas are often in their overall poor health due to malnutrition, ongoing infection, and their primary condition making surgical management and post-operative care challenging. A multidisciplinary discussion among aerodigestive specialists and involvement of palliative care team is desired during the management of these patients. A computed tomography (CT) of a neck or a chest is commonly used during initial evaluation of patients. The diagnosis of a fistula should be confirmed by barium esophagram, or direct endoscopic inspection by esophagogastroduodenoscopy (EGD) or bronchoscopy to determine the suitable management. Location and length of TEF with its distance from the carina and larynx, presence of esophageal obstruction and airway compromise are important attributes to be evaluated. If critical airway obstruction is present, a therapeutic bronchoscopy with recanalization and stent placement should be followed by esophageal stent placement. In those with poor nutrition status an alternative way of enteral and parenteral nutrition should be considered (*Figure 1*).

Esophageal stenting

Esophageal stent placement has been used in both benign and malignancy related fistulas. Many TEFs located within the mid-to-distal trachea or bronchial airways can often be managed by esophageal stenting alone. Endoscopic treatment of malignant disease with SEM stents has become the mainstay in treating these patients (*Figure 1*). The stents are typically placed under fluoroscopic guidance often with the use of radiopaque makers to identify landmarks as well as the lesion. A guidewire is deployed under endoscopic guidance and fluoroscopy is used for stent positioning and deployment. The stent is ideally sized to extend one to two centimeters beyond the fistula (9). When the fistulas are located too high in the first third of the esophagus or contain gastric mucosa (post-esophagectomy) esophageal stenting may not be feasible.

Table 2 Summary of the selected studies describing the management of tracheoesophageal fistulas

Study	Population	Number of patients	Intervention	Outcome	Notes
Esophageal stenting					
Chen 2021 (8)	Retrospective review of esophageal squamous carcinoma patients with TEFs	86 patients	30 patients with esophageal metallic stent *vs.* 35 patients with feeding G/J	Overall survival: stent group 144.8 days *vs.* 76.6 in G/J group, P=0.007	More patients in stenting group were able to receive chemotherapy within 30 days (53% *vs.* 14%)
Qingxia 2023 (9)	Retrospective review of patients with malignant TEFs	288 patients	194 patients with stents (170 esophageal, 24 tracheal) *vs.* 94 patients treated conservatively	Esophageal stent improved fistula closure (OR =0.010; 95% CI: 0.004–0.030; P<0.001) as did tracheal stent (OR =0.003; 95% CI: 0.000–0.042; P<0.001)	Pulmonary infection less at one month in stent group (33.5% *vs.* 77%, P<0.001); 82/170 patients had complications in esophageal stent group, 11/24 in tracheal stent group
Yamamoto 2023 (10)	Propensity matched pairs of malignant TEFs from inpatient database	43 patients	Esophageal bypass surgery *vs.* SEMS	Decreased respiratory complications in stenting (OR =0.077; P=0.007)	Anticancer therapy delayed in bypass group (25 *vs.* 7 days, P=0.003)
Sumiyoshi 2003 (11)	Retrospective review of malignant TEFs or dysphagia in esophageal cancer	22 patients, 13 with TEFs	SEMS placement	100% fistula closure; median survival 67 days	17 patients had T4 tumors, 8 with invasion into aorta of whom 6 died from massive hemorrhage
Debordeau 2018 (12)	Retrospective review of benign TEFs	22 patients	21 esophageal stents, 8 over the scope clips, 7 combined therapy	Endoscopic success 45.5% (67% in punctiform, 50% in medium and 14% in large TEFs), functional success 55%	Orifice size associated with mortality
Airway stenting					
Chung 2012 (13)	Retrospective review of esophageal cancer with TEFs	59 patients	31 patients with and 28 patients without SEMS	Improved overall survival 69 *vs.* 21 days (P=0.004; HR =0.56; 95% CI: 0.31–0.99)	–
Bai 2022 (14)	Retrospective review of malignant CAO or TEFs receiving SEMS placement	106 (82 CAOs, 24 TEFs)	24 patients with SEMS	3-month survival rate 45.8%	50% had symptomatic improvement
Dual stenting					
Freitag 1996 (15)	Retrospective review of malignant TEFs	30 patients	12 tracheal, 18 dual stents	Survival in dual stent groups was significantly higher (110.2 *vs.* 23.8 days, P=0.0027)	–
Herth 2010 (16)	Prospective study for 3 years of malignant TEFs	112 patients	65 airway stents, 37 esophageal stents, 10 dual stents	Mean survival for airway stent was lower than esophageal or dual stenting: 219.1 (95% CI: 197.3–240.9) *vs.* 262.8 (95% CI: 244.4–381.3) *vs.* 252.9 days (95% CI: 192.9–312.9)	Initial choice of stent placement based on presence of stenosis
Ke 2015 (17)	Retrospective review of SEMS and silicone airway stenting for TEFs	61 patients	43 SEMS and 18 silicone stents	Metallic stents: 28 (65%) complete response, 15 (35%) partial response Silicone stents: 13 (72%) complete response, 5 (28%) partial response Dual stents: 24/25 metallic stents complete response, 10/10 silicone stents complete response	–
Khan 2020 (18)	Retrospective review of esophageal cancer and dual stenting	29 patients (24 CAO, 5 TEFs)	Dual stenting	Median survival 97 days, survival prolonged for isolated TEFs compared to other groups	–
Bi 2019 (19)	Retrospective review of malignant tracheobronchial and esophageal diseases requiring combined stenting	35 patients	26 instances of stents for TEFs	Mean Hugh-Jones grade decreased (from 3.0 to 1.3, P<0.0001); mean dysphagia score decreased (from 3.2 to 1.2, P<0.0001)	1-, 3-, 5-year survival rates for all with 82.%, 78.8% and 78.8%
Suturing/clipping					
Jin 2022 (20)	Retrospective review of gastrointestinal fistulas undergoing endosuturing	20 patients, 12 TEFs	Endosuturing with APC; 50% received additional clip fixation, 10% stenting	TEFs more persistent than other GI fistulas (HR =3.378; 95% CI: 1.13–10.13; P<0.01); sustained fistula closure in 5 patients	–
Mahmoud 2022 (21)	Retrospective review of GI defects closed with X-tack system	93 patients, 8 TEFs	–	2/8 fistula closures (both also received SEMS)	–
Kobara 2019 (22)	Review of GI defect clipping in 30 articles	1,517 cases, 388 fistulas	Over-the-scope-clip	Clinical success rate 51.5%	–
Haito-Chavez 2014 (23)	Retrospective review of over-the-scope clipping for GI defects (benign and malignant)	188 patients, 16 TEFs	Over-the-scope-clipping	Clinical success rate 42.9% at ~121 days	–
Law 2015 (24)	Retrospective review of benign TEFs	47 patients, 3 TEFs	Over-the-scope-clipping	Clinical success rate 100% (1/1)	All patients: 53% sustained fistula closer at media 178 days

Table 2 (*comtinued*)

Table 2 (*continued*)

Study	Population	Number of patients	Intervention	Outcome	Notes
Occluding devices					
Rabenstein 2006 (25)	Case report of VSD occlude for nonmalignant TEF	1 patient	VSD occluder	Initial technical success; partial clinical response at 10 weeks, 6 months and 1 year	Complications: slight dislocation, minor hemoptysis
Jiang 2015 (26)	Review of case reports of ASD occluder devices used on TEFs	5 patients	ASD occluder	5/5 successful closure	3/5 had migration of device
Cohen-Atsmoni 2015 (27)	Review of mechanically ventilated patients who received ASD occluders for TEFs	2 patients	ASD occluder	2/2 technical success; 6 months clinical success and 2 weeks clinical success before reoccurrence	–
Traina 2018 (28)	Case report of chronically ventilated patient with recurrence of surgically closed tracheostomy related TEF	1 patient	Type of septal occluder not specified	Previously also failed treatment with acrylic glue. Initial technical success confirmed at 4 weeks. Asymptomatic at 12-month follow-up	–
Siboni 2022 (29)	Case report of the 3-D computed tomography utilization for occluder sizing	1 patient	ASD occluder	Initial technical success confirmed day 3 and week 4; complete clinical success at day 5 and at 4 months	–
Bawaadam 2022 (30)	Case report of a silicone septal nasal occluding device for benign TEF 1 cm below the vocal cords	1 patient	Silicone 2 cm septal nasal occluder	Successful closure confirmed by a barium swallow 1 week later. Asymptomatic at 12-month follow-up	–
Zhu 2022 (31)	Case report of a novel dumbbell-shaped occlude placed for chronic TEF	1 patient	A newly developed dumbbell-shaped occlude without protrusions	Successful closure confirmed clinically at 2 days. Closure confirmed by endoscopy and contrast examination, 4-month follow-up	–
Tissue adhesives					
Sharma 2018 (32)	Case report, TEF after chemoradiotherapy for esophageal carcinoma	1 patient	Trans-tracheal glue injection	Clinical success	–
Goh 1994 (33)	Case report, TEF from esophageal carcinoma	1 patient	Endoscopic histoacryl glue application	Clinical success	–
Truong 2004 (34)	Retrospective review of anastomosis leaks or fistulas after upper GI surgery	9 patients	Vicryl mesh sealed with fibrin glue	7/9 had closure after two endoscopic treatments	–
Scappaticci 2004 (35)	Case report, iatrogenic TEF	1 patient	Bronchoscopic application of Tissucol	Fistula closure at 10 days	–
Alcohol ablation					
Finley 2011 (36)	Retrospective review of TEFs from radiation therapy	7 patients	Silver nitrate and dehydrated alcohol injections	6/7 fistula closure	4 patients required multiple ablations
Platelet rich plasma					
Damien 2022 (37)	Retrospective review, TEFs after laryngectomy	2 patients	PRP injection	2/2 fistula closure	–
Han 2024 (38)	Case report, TEF after cancer resection	1 patient	PRP injection after stent failure	Fistula closure at 3 m	–
Wu 2021 (39)	Case series	3 patients	PRP injection	Fistula closure in 16–18 weeks	1 patient also received stent
Bioprosthetic					
Mahajan 2018 (40)	Case report, TEF after infection	1 patient	Y stent with surrounding Acell®	Fistula closure at 10 days	–
Cairo 2017 (41)	Case report, neonate with recurrent esophageal anastomotic stricture post TEF repair	1 patient	Esophageal stent with urinary bladder matrix sutured on esophageal stent repeatably	Clinical success with subsequent removal of the esophageal stent after 4 months	–

APC, argon plasma coagulation; ASO, atrial septal defect; CAO, central airway obstruction; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; OR, odds ratio; PRP, platelet-rich plasma; SEMS, self-expandable metallic stent; TEF, tracheoesophageal fistula; VSD, ventricular septal defect.

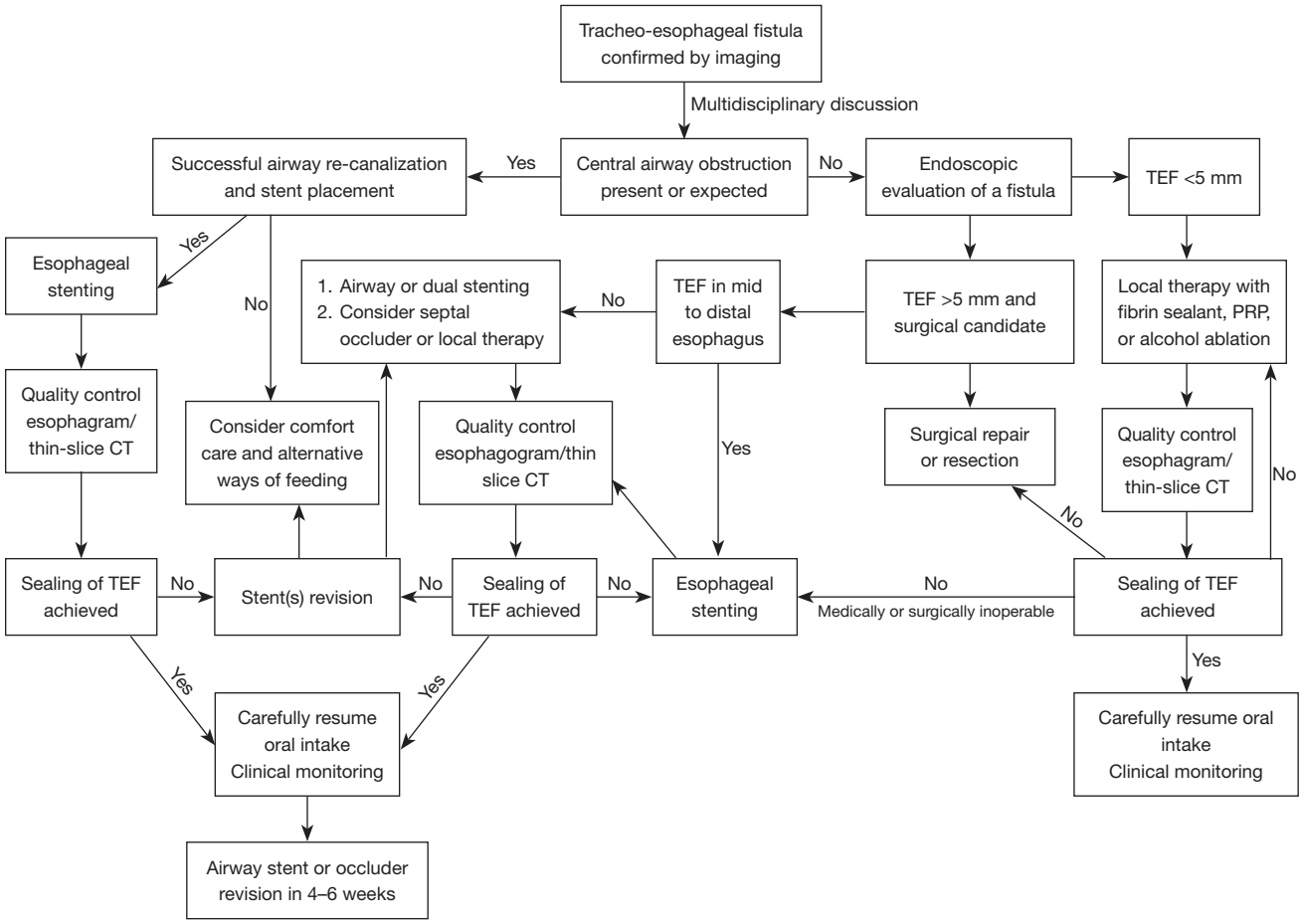

Figure 1 Proposed algorithm for management of tracheo-esophageal fistulas regardless of their etiology. CT, computed tomography; TEF, tracheoesophageal fistula.

In one of the largest comparative studies by Chen *et al.*, 86 patients with malignancy related TEFs were followed; 30 patients received esophageal metallic stent (five of which also received a tracheal stent) and 35 patients received gastrostomy or jejunostomy tubes. Overall survival was 145 days in patients receiving stents, compared to 77 days in those without stenting (8). In a retrospective review of 288 patients with malignancy related TEFs (194 patients having received stents compared to the 94 without), patients who received stents showed improvements in performance scores, pulmonary infections and fistula closure compared to those patients receiving conservative therapy (9). Esophageal stenting has also been compared to esophageal bypass surgery in a propensity matched analysis (10). This study showed a decrease in respiratory complications, length of stay, and time to antineoplastic therapies in the stenting group. Esophageal stents have also been placed after chemoradiotherapy with success in palliating symptoms; however, patients with T4 tumors involving vascular invasion receiving stenting had an increased risk of fatal hemorrhage (11). Complications of esophageal stent placement can include esophageal perforation, propagation of existing TEF, development of TEF, hemorrhage, tracheal compression, stent migration, worsening reflux, granulation tissue growth into stent and chest pain (11,15). Esophageal stents have also been assessed in TEFs of benign etiologies. Debordeau *et al.* performed a retrospective analysis of 22 patients who received endoscopic therapy. Fourteen patients had stent placement, seven had stent and over-the-scope clipping, and one had clipping only. Successful closure was seen in 45.5% of cases within 6 months. Ten patients had failure of fistula closure including six patients who died during follow-up (12). Studies looking at both benign and malignant causes of TEFs showed similar technical and

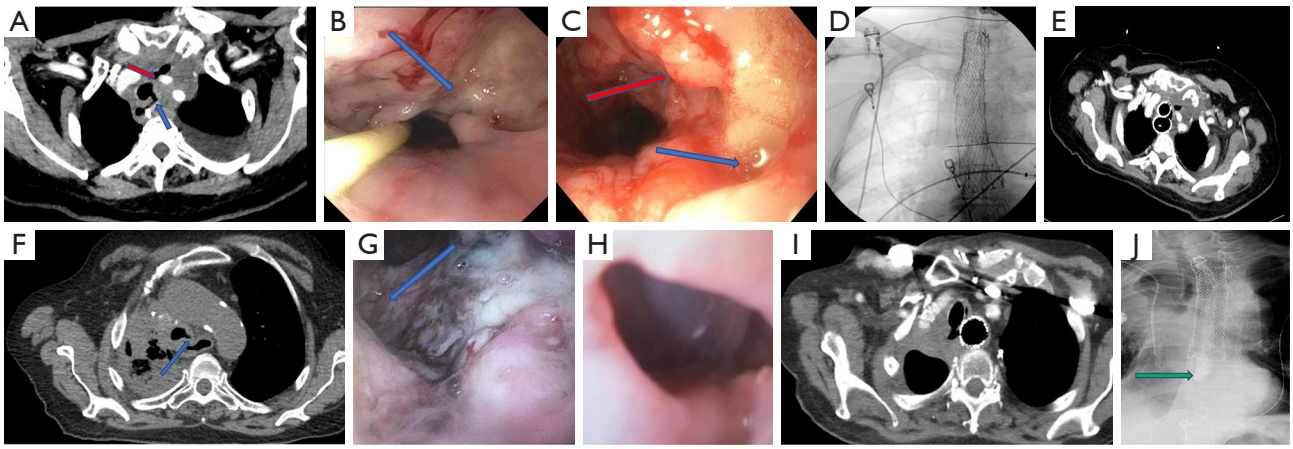

Figure 2 Two case reports of dual stenting for TEF with a quality control evaluation. Case 1 top row—(A) CT of the chest with a malignant trachea-esophageal (blue arrow) and tracheo-mediastinal (red arrow) fistulas. (B) Endoscopic image with nasogastric tube in place and visible TEF (blue arrow). (C) Bronchoscopic image with visible TEF (blue arrow) and treacheo-mediastinal fistula (red arrow). (D) Fluoroscopy image post stents placement. (E) Quality control CT chest with visible fully covered metallic stent size 16 mm × 60 mm in the proximal trachea and fully covered 16 mm × 120 mm metallic stent in the proximal esophagus. Case 2 lower row—(F) CT chest with a malignant trachea-esophageal fistula located 1.5 cm from the carina (blue arrow) and narrowing of the distal trachea. (G) Bronchoscopic image and visible TEF (blue arrow). (H) Endoscopic image with visible silicone Y stent providing incomplete seal of the fistulous tract. (I) Quality control CT chest with silicone Y stent size 16–13–13 mm in the trachea and fully covered stent size 23 mm × 120 mm in the esophagus. (J) Quality control esophagram showing a contrast passing distally through the esophageal stent (green arrow). CT, computed tomography; TEF, tracheoesophageal fistula.

clinical success rates (42). Proximal fistulas showed lower rates of both technical and clinical success (42,43). Despite its challenges, esophageal stenting remains an attractive minimally invasive therapeutic option as it decreases symptoms, complications, and likely improve overall survival in both benign and malignant etiologies.

Airway stents and dual stenting

Esophageal stenting alone is generally preferred over airway stenting alone, as the morphology of esophagus often allows for a better seal of the fistula and carries less risk of airway obstruction. Nonetheless, airway stenting is needed in cases of malignant airway obstruction, predicted airway compromise by esophageal stenting or in cases with inability to adequately seal the fistula from an esophageal approach. *Figure 2A-2E* and *Figure 2F-2J* represent two cases of malignant airway obstruction and TEF. Both patients were treated with dual stenting. See the figure legend for the details of the cases. Direct visualization during bronchoscopy helps with selection and sizing of a stent. SEM stents conform to airway shape better provide better seal of TEF. Silicone stents have studs on their surface allowing for better secretion clearance and preventing migration. On the other hand, those studs may stand in the way of a proper sealing. Both stent types come in tubular and Y shape, in different sizes, and with different types of deployment mechanisms. Deployment of silicone stents requires rigid bronchoscopy. SEM stent can be deployed over the guidewire or through the working channel of a flexible bronchoscope. There are no comparative studies of different types of airway stents for TEFs and therefore general stenting principles apply:

- Stent should ideally extent 2 cm proximal and distal to TEF or to extrinsic compression allowing for a good seal and providing sufficient airway stability.
- Minimal required amount of airway mucosa should be covered by a stent to allow proper mucosal clearance.
- Y shaped stents (SEM or silicone) should be reserved for lesions/obstructions involving or close to a main carina.
- Oversizing of a stent for more than 20% of airway lumen should be avoided to prevent propagation of a fistulous tract 5. The individual qualities of different stents should be considered.

Similar to esophageal stents, airway stents can be

deployed with the assistance of guidewire and fluoroscopy. Stent deployment under direct visualization via rigid bronchoscopy or through the working channel of a flexible bronchoscope allows for a better positioning as well as prevents complications related to inappropriate deployment (e.g., into fistulous tract). In a case-control study, 59 patients with TEF due to esophageal cancer were studied, including 31 patients who received tracheal SEM stent for malignancy related TEFs. Airway stenting [adjusted odds ratio (OR) =5.2], performance status (adjusted OR =6.1), and further treatment (adjusted OR =8.7) positively impacted the survival (13). A retrospective study that examined the utility of SEM stents for both central airway obstruction and TEFs secondary to malignancy showed that half of the 24 TEF patients had symptomatic improvement with a 3-month survival rate of 45.8% (14). Further innovative approaches continue to be seen. In one case report, a Y shaped SEM stent was threaded over a three-dimensional (3-D) printed model of the airway and was customized to the patient's airway (44).

Combining esophageal and airway stents has traditionally been avoided because of the theoretical risk of developing new TEF or propagating the existing one. Three studies compared outcomes between tracheal stent alone *vs.* dual stenting and all showed better symptomatic response and better survival in groups with both stents (15-17). On the other hand, in a single center retrospective analysis of 216 patients with malignant esophageal obstruction managed by endoscopic stenting, 15 patients experienced fatal hematemesis. The mean time to massive bleeding was 16.9 after esophageal stent insertion. The presence of TEF (OR =9.1) and concomitant tracheal stent (OR, 7.9) were found to be two statistically significant risk factors associated with the hemorrhage (13). Khan *et al.* described the use of combined airway and esophageal stenting in a prospective study of 29 patients with esophageal cancer and airway involvement, including five patients with TEF present. Authors reported symptomatic improvement in all patients and did not report major hemorrhage or developing or propagating of TEFs in the 4-year study period (18). Another single center retrospective review of 35 patients receiving combined stenting for malignant tracheoesophageal disease including fistulas and stenosis demonstrated symptom improvement without the development of *de novo* fistulas at the stenting sites. Restenosis (7.7%) and stent migration (2.6%) were the most common complications of the airway stents. Airway compression with esophageal stent being placed prior to an airway stent (7%) and stent migrations (7%) were the most common complication of the esophageal stenting (19). In a novel case report, self-made twin magnetic stents were inserted via a tracheostomy. The magnets were used to fix both airway and esophageal stents to each other through the benign TEF opening to prevent migration. The patient was able to start oral nutrition, and the stents remained in place for 14 months as a bridge to surgical intervention (45).

Endoscopic suturing and clipping

Used initially for the treatment or prevention of post-procedural bleeding and defects, endoscopic suturing and clipping have also been used for the treatment of TEFs. These devices are either deployed over the scope or through the working channel of an endoscope. They have commonly been reported as part of a multi-modal approach to fistula management. Jin *et al.* reviewed 20 patients with fistulas of aerodigestive tract, including 12 with TEFs. Seven of those failed the previous therapy with an esophageal stent. All patients had a closure attempted via endoscopic suturing and received additional argon plasma coagulation. Half of the patients received additional clipping and two of them additional esophageal stent. The immediate endoscopic success for fistula closure was 100%, but sustained fistula closure at 3 months was seen in only 25% of patients. TEFs had shorter time to dehiscence than other fistula etiologies [hazard ratio (HR) =3.378] (20). Mahmoud *et al.* described over the scope suture placement in eight patients with benign TEFs; however, only two patients had successful fistula closure. Both patients with successful closure had also received subsequent SEM stents (21). In a larger retrospective review of endoscopic clipping over a half of 388 patients with TEFs had successful closure at one month (22). Two case series reported similar sustainability despite high technical success at the initial placement (23,24). It has been theorized that denudement or resection of the fistula's mucosa may improve clinical success (46), as the necrotic and inflamed tissue at the site likely contributes to failure. Overall, minimal complications or adverse events have been reported with suturing and clipping techniques making it a safe approach. Complications may include pain, bleeding at the clipping/suturing site, luminal stenosis, and micro-perforation and are mild in nature (21,22). These techniques also do not have the same associations with development or worsening of fistulas, which may make them an attractive initial management approach. Endoscopic suturing for fixation

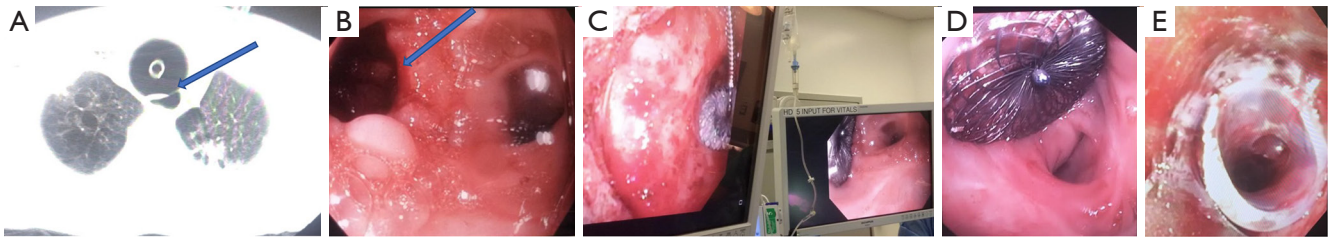

Figure 3 A case of benign TEF caused by endotracheal tube cuff overinflation, managed with an ASD occluder size 23–10–18 mm. (A) CT of the chest with dilated trachea and visible TEF fistula (blue arrow). (B) Endoscopic view from the esophagus with visible TEF (blue arrow). (C) Bronchoscopic view (left) and endoscopic view (right) during placement of the ASD occluder. (D) Endoscopic view post ASD occlude placement. (E) T-tube stent placed on top of the ASD occluder device causing minimal airway lumen compromise (case report and images are courtesy of Dr. Eugene Shostak). ASD, atrial septal device; CT, computed tomography; TEF, tracheoesophageal fistula.

has been shown to have an important utility in preventing esophageal stent migration. In a retrospective study of 125 patients who had fully covered SEM stent placed, stent migration was reduced from 33% to 16% after endoscopic suturing, including patients who had prior episodes of stent migration (47).

Occluding devices

Another more recent approach to TEF management includes the off-label use of occluding devices, namely cardiac septal defect occluders such as the Amplatzer® device (Abbott Laboratories, Chicago, IL, USA). These devices have two self-expanding umbrellas connected by a smaller waist that traverses a fistula. The left atrial/ventricular umbrella is larger in diameter than the right one and should therefore cover the esophageal site to avoid unnecessary airway narrowing. A guidewire is deployed across the fistula, either from the trachea or the esophagus, and then used to deploy the sheath (*Figure 3*). The occluder can then be deployed under direct visualization and fluoroscopy. Rabenstein *et al.* first reported the use of ventricular septal defect using bronchoscopy and esophagoscopy (25). Since then, there have been other case reports of successful deployment of these devices (atrial or ventricular) with improvement in symptoms and successful healing of the fistulas (26). They have also been deployed successfully in chronically ventilated patients (27,28). 3-D CT with holographic assessment has been used to aid in appropriate sizing of the device (42). Dislodgement and migration of an occluder into the airway after epithelization of a fistula seems like the most common complication and patient can present with severe airway obstruction (25,48,49). Buitrago *et al.* reported a case of fatal hemoptysis one month after the occluder placement (50). The use of cardiac septal defect occluders should be used with caution and close follow-up of the patients is strongly warranted. It seems prudent to remove the septal occluder once there is epithelization of the umbrella and closure of the fistula is achieved to prevent potential complications. Other similar approaches have been described using nasal septal buttons (30) and also a novel dumb-bell shaped occluder (31).

Tissue adhesives

Application of tissue adhesives to TEFs via endoscopic catheter has been reported with general success in pediatric patients (51). Fibrin sealant (e.g., Tisseel®, Baxter, Deerfield, IL, USA) and cyanoacrylate glues (e.g., Histoacryl®, B. Braun, Melsungen, Germany) have both been used. Fewer cases have been reported in adults, but both bronchoscopic and endoscopic approaches have been used. Depending on the characteristics of the fistula, a bronchoscopic approach has sometimes been preferred to prevent leakage of glue into the airway (32). These agents can also be used to treat very proximal lesions where stent placement may be difficult (33). A series of nine cases described endoscopic application of fibrin glue in combination with Vicryl mesh for larger upper gastrointestinal post-surgical leaks and fistulas. Two patients had TEF, one patient showed complete healing of the bronchoesophageal fistula after two applications, while the other had persistent TEF (34). Successful gluing has also been described in a mechanically ventilated patient who was high risk for surgical intervention (35). The broad availability and tolerability may make this a reasonable approach for small fistulas or in patients with contraindications to more invasive therapies.

Alcohol ablation

A combination of silver nitrate and dehydrated alcohol has been described to treat a group of seven patients with small (<5 millimeter) bronchopleural or TEFs, two of whom had TEFs secondary to radiation therapy. Silver nitrate was brushed over the site followed by an injection of dehydrated alcohol (approximately 0.25–0.5 mL per injection) around the fistula. Four patients required multiple ablations. One TEF had resolution while another had persistent fistula requiring an airway stent. All of the bronchopleural fistulas resolved (36). While widely available, more TEF specific efficacy data is needed before broader application of this technique.

Platelet rich plasma

Autologous platelet-rich plasma (PRP) has been used to promote wound healing in many medical conditions. The patient's own blood is centrifuged to create the PRP and is injected submucosally around a fistulous tract. In a report of two cases of persistent TEFs after laryngectomy that failed both conservative and surgical approaches, PRP was injected in two to three sessions. Both patients had complete resolution of their fistulas on methylene blue dye tests within 3 weeks (37). An endoscopic approach has also been reported in a patient with TEF and esophageal stenosis after resection for cancer. This patient was first treated with PRP injection, a coated metal stent, acid suppression, and antibiotics. On one month follow-up, the fistula had improved, but the stent was removed due to a foreign body sensation. The patient received two subsequent injections and had a completely healed fistula with resolution of symptoms in 3 months (38). A bronchoscopic approach has been described in 3 patients with bronchopleural fistula after lobectomy. Each patient received between two and six PRP injections with one patient also requiring a membrane covered stent in the trachea. The fistulas resolved within 15 to 18 weeks on follow-up (39). Although promising case reports, further research is required before this treatment approach is used more frequently and its utility may be limited to small defects.

Bioprosthetics

The use of bioprosthetic materials such as acellular tissue matrix (e.g., Alloderm®, AbbVie, Branchburg, NJ, USA) and aortic homograph for TEFs have largely been described in surgical contexts (52-54). Endoscopic applications have been less frequently described. In 2018, Mahajan *et al.* reported a 66-year-old female with history of histoplasmosis capsulatum infection with a calcified subcarinal node and an associated obstructing polyp of the right mainstem bronchus (40). One year after excision of her polyp, she returned with symptoms from a 2 cm defect along the medial wall of her right mainstem. She was initially treated with Dumon™ silicone Y stent (Boston Medical Products, Shrewsbury, MA, USA) and a fully covered metallic esophageal stent. On 8-week follow-up, the fistula was improved but persistent. A bronchoscope was passed around the Y stent to placed four sheets of ACell® (ACell Inc., Columbia, MD, USA) decellularized porcine urinary bladder matrix at the site using forceps. Ten days later, there was complete resolution of the TEF on surveillance bronchoscopy followed by removal of both stents one week later. She had continued resolution on follow-up at 10 months. An esophageal approach has also been described in a neonate with recurrent anastomotic stricture after esophageal atresia repair with strips of urinary bladder matrix sutured to the outside of an esophageal stent (41). Research on other substrates such as polymeric scaffolds made from natural and synthetic materials is underway (55). Their use may be appealing for larger defects and areas that are difficult to stent.

Quality control and follow-up

If persistent and clinically significant leak is suspected despite the initial treatment, repeat imaging with thin-slice CT or contrast esophagograms are preferred methods over an endoscopic evaluation. Small residual TEFs and inadequate seal can be difficult to visualize during endoscopic examination due to mucosal edema caused by presence of a foreign body or previous instrumentation. Stent revision is the next step when the persistent leak is confirmed. Alternative forms of feeding and comfort care measures only should be considered for chronic inoperable fistulas which failed the endoscopic management. Bronchoscopic airway stent revision to detect common stent related complications such as mucus plugging, tumor ingrowth, granulation tissue is usually recommended at 4–6 weeks after the insertion (56) while minding the overall clinical status of a patient.

Discussion

TEFs are a highly morbid condition with complex

presentations that require variable approaches. Esophageal stenting with SEM stent is often able to be used alone as the initial endoscopic approach for both benign and malignancy associated fistulas. Smaller fistulas can be considered for more local therapies instead, such as sealant, platelet rich plasma or alcohol ablation. If central airway obstruction is present, airway or dual stenting might be the best first step. If fistula control is not achieved with esopahgeal stent and stent revision, additional airway stent, occluder device or palliation can be discussed based on the patient's case and their needs.

The literature review of the endoscopic management of TEFs consists of small studies, case series often form single centers, case reports and experts' opinions. This is likely further limited by a publication bias of only successful techniques especially amongst case reports. Large randomized studies comparing different methods are lacking. Our review was also limited to English articles. A thorough search was performed but additional reports in other databases may be present. The scope of our article was limited to an endoscopists' perspective and does not include surgical techniques or such unique circumstances as post-laryngectomy fistulas. Although unable to confidently add a level of recommendation to the individual endoscopic techniques the narrative review provides a solid base for designing the future research in this area.

Conclusions

TEF possesses therapeutic challenges whether they are of malignant or benign origin. As this process is often accompanied by poor nutrition, recurrent infections and declining functional status, alternatives to surgery are an important consideration in management. A multidisciplinary approach weighing in surgical, endoscopic, and palliative options is often lacking but when present, is an important part of developing management plans for these complex patients. The early involvement of the appropriate aerodigestive and palliative specialists as the local resources allow helps with the complexity of these patients. Despite emerging new endoscopic techniques esophageal stenting alone remains the first-line treatment for endoscopic management of TEFs. Airway stenting is reserved for selected conditions of an inadequate fistula sealing or when a malignant or iatrogenic airway obstruction is present. Other non-standard approaches and off-label use of different devices should be used with caution and after thorough discussion with a patient and their family.

There is still much that is not understood about the management of TEFs with many opportunities for further research. More rigorous comparative studies would lead to better understanding of the techniques with the best outcomes and are an important step in future studies. New innovation in devices would help to improve closure of fistulas, ease of placement and decrease the complication rate. As the science of tissue scaffolding and other biological interventions improves, this approach also could offer a more enduring response with fewer complications. While uncommon, the life threatening and debilitating nature of TEFs make them an important focus of future study.

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Footnote

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from the patients or the relatives after all reasonable attempts were made.

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Review Article

Surgical approaches for thymectomy: a narrative review

Yash Vaidya[1]^, Andreas Polycarpou[1], Sophia Gibbs[1]^, Madhuri Rao[2]^, Amit Bhargava[2]^, Rafael Andrade[2], Ilitch Diaz-Gutierrez[2]^

[1]Division of Cardiothoracic Surgery, Department of Surgery, University of Minnesota, Minneapolis, MN, USA; [2]Division of Thoracic and Foregut Surgery, Department of Surgery, University of Minnesota, Minneapolis, MN, USA

Contributions: (I) Conception and design: Y Vaidya, A Polycarpou, I Diaz-Gutierrez; (II) Administrative support: A Bhargava, R Andrade; (III) Provision of study materials or patients: M Rao, A Bhargava, R Andrade, I Diaz-Gutierrez; (IV) Collection and assembly of data: Y Vaidya, A Polycarpou, S Gibbs; (V) Data analysis and interpretation: Y Vaidya, A Polycarpou, I Diaz-Gutierrez; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ilitch Diaz-Gutierrez, MD. Division of Thoracic and Foregut Surgery, Department of Surgery, University of Minnesota, 420 Delaware Street SE, MMC 207, Minneapolis, MN 55455, USA. Email: ilitch@umn.edu.

Background and Objective: Thymectomy continues to be a standard treatment strategy for patients with thymic neoplasms and myasthenia gravis. The total thymectomies performed has exponentially increased by 69.8% between 2012 and 2019. Trans-sternal and minimally invasive thymectomy increased by 62.8% and 83.7%, respectively. Our objective is to provide a narrative overview of the various approaches of thymectomy. We have briefly described the indications for thymectomy, discussed important preoperative considerations and an operative description of the different techniques of the procedure. We have aimed to summarize the pros and cons of each approach and narrated the technique we have adopted at the University of Minnesota.

Methods: A literature search was conducted encompassing original full-length articles, meta-analyses, review articles and case reports up to July 2024 from the MEDLINE and Google Scholar databases.

Key Content and Findings: Complete surgical resection remains the goal to decrease the risk of recurrence for non-myasthenic thymomas and thymic carcinomas. Surgical procedures have evolved from traditional open approaches to a wide variety of minimally invasive methods. A variety of factors specific to the tumor, patient and surgeon have to be considered while planning a thymectomy.

Conclusions: As of today, there is no consensus on the best surgical technique, with each approach providing specific pros and cons. Each technique may be a viable option in the management of thymic pathologies, thus preoperative evaluation in patients is necessary to optimize prognosis and outcomes.

Keywords: Thymectomy; subxiphoid subcostal thymectomy; thoracoscopic thymectomy; transcervical thymectomy

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^ ORCID: Yash Vaidya, 0000-0002-2522-1104; Sophia Gibbs, 0009-0004-5889-9474; Madhuri Rao, 0000-0001-8934-275X; Amit Bhargava, 0000-0003-4586-8340; Ilitch Diaz-Gutierrez, 0000-0002-6196-6955.

Table 1 The search strategy summary

Items	Specification
Date of search	Up to July 31, 2024
Databases and other sources searched	MEDLINE, Google Scholar
Search terms used	"thymectomy", "minimally invasive thymectomy", "thoracoscopic thymectomy", "subxiphoid thymectomy", "robotic thymectomy" or any combination thereof
Timeframe	Up to July 31, 2024
Inclusion and exclusion criteria	All English language articles, including original full-length articles, meta-analyses, review articles and case reports were included. Any articles without details on thymectomy approach were excluded
Selection process	All articles selected using the above criteria were independently reviewed by all authors. Consensus was obtained after reviewing the inclusion and exclusion criteria set forth

Introduction

Since 1998 the incidence of thymectomies has continued to rise in the United States, with an estimate of 1,000 cases performed every year (1,2). The two primary indications include thymic neoplasms and non-thymomatous myasthenia gravis (MG). Throughout the years, advancements in surgical techniques, particularly minimally invasive methods, have revolutionized the way care is delivered. However, due to the lack of consensus regarding the best surgical approach to thymectomy, it is imperative to individualize the surgical strategy based on the clinical presentation and anatomical features. This includes a comprehensive assessment of the size and location of the tumor, invasion to adjacent structures, history of neoadjuvant therapy, anesthetic considerations, evaluation of the merits and pitfalls for each surgical approach, and individual surgeon's experience.

Thymic neoplasms are a rare entity. Population studies have shown an incidence of 2.5 to 5 per million, though lower rates are reported from the Surveillance Epidemiology and End Results (SEER) database (3-5). This has been attributed to missing smaller thymomas, which were previously thought to be benign (6). Despite the discrepancy in incidence rates, thymomas are the most common mediastinal tumor in adults (7) and comprise up to 1.5% of all mediastinal neoplasms (8). This group includes thymomas, neuroendocrine tumors of the thymus (NETT) and thymic carcinomas, with the latter comprising 14% of all thymic neoplasms (9-11). With incomplete resection, there is an increased risk of local recurrence for non-myasthenic thymomas and thymic carcinomas (8,12). Therefore, complete oncologic resection is a crucial prognostic factor for thymic tumors. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-38/rc).

Methods

A search was conducted on the MEDLINE and Google Scholar databases. All articles published until July 2024 were considered. Search terms included "thymectomy", "minimally invasive thymectomy", "thoracoscopic thymectomy", "subxiphoid thymectomy", "robotic thymectomy" or any combination thereof. All article types including original full-length articles, meta-analyses, review articles and case reports were included (*Table 1*).

Clinical presentation

For patients with an indeterminate anterior mediastinal mass, the clinical history should focus primarily on identifying symptoms related to MG (such as weakness, diplopia, ptosis), B symptoms associated with lymphoma (fever, night sweats and weight loss), or symptoms suggestive of thyroid disease. Although some thymomas may be asymptomatic, approximately one third experience chest pain, cough, dyspnea, and up to half will additionally suffer from parathymic syndromes such as MG (7). With larger tumors, patients may experience symptoms related to invasion/compression of adjacent structures. When the superior vena cava is compromised, patients may present with headaches, upper body edema, distended neck veins, coughing, dyspnea and orthopnea. A symptom of particular concern is orthopnea, which may be indicative of a large anterior mediastinal tumor compressing on the trachea.

MG

In 2021 the prevalence of MG in the United States was estimated to be 37 per 100,000 persons, and globally it has been increasing in prevalence over the last decade (13). Furthermore, 15% of MG patients are associated with having a thymoma (7). Complete resection should be targeted in all thymoma cases regardless of MG type. Additionally, even in the absence of a thymoma, thymectomies still hold benefits as a treatment option for MG and acetylcholine receptor (AChR) antibody positive patients (14). A clinical trial in 2016 found transsternal thymectomy and alternate day prednisone to have more favorable outcomes than treating patients with prednisone alone, and had fewer recurrences after 3 years of follow-up (15). This study also demonstrated that patients, who underwent thymectomy, required fewer immunosuppressants and daily doses of prednisone. In terms of indications for thymectomies in MG, age is not typically an exclusion factor, and all thymomas, regardless of MG type, should be resected within the first 3 years of diagnosis if possible (16). Preoperative imaging with computed tomography (CT) can be used to help determine the course of treatment. CT scan can identify thymic hyperplasia, which has been shown to be a favorable predictor of improved outcomes (17). Some of the benefits following surgical treatment of MG include relieving weakness and averting potential complications from immunosuppressive therapy (14).

An added benefit of surgical treatment for thymomas, and specifically thymic carcinomas, is the ability to examine the pleural surfaces for metastases, and if possible, concomitant resection of such metastases during the thymectomy (18). Complete resection of such lesions has been associated with lower rate of complications and improved recovery (19,20).

Based on the clinical presentation and anatomy of the thymoma, the surgeon can make important treatment decisions. This includes identifying those patients with undiagnosed or uncontrolled MG that need referral to a neurologist prior to surgical resection or discovering patients with large tumors that may not be appropriate for a minimally invasive approach.

Anesthesia considerations

Careful preoperative evaluation and optimization of medical therapy are paramount in patients with MG, to reduce the risk of respiratory failure, aspiration, and myasthenic crisis. Specifically, anticholinesterase inhibitors such as pyridostigmine, and immunosuppressants when appropriate, should be continued until the day of surgery. Muscle relaxants are minimized or avoided when possible. Reducing the dose of glucocorticoids can help diminish the risk of postoperative infectious and wound healing complications (14). Consideration should be given to preoperative plasmapheresis or intravenous immunoglobulin (IVIG) therapy for patients at high preoperative risk for respiratory complications, such as those with preoperative neuromuscular weakness (21,22). Preoperative spirometry is a useful tool to assist in identifying such at risk patients (23).

An important preoperative concern is determining whether the patient can lay flat without orthopnea, since the presence of this symptom is worrisome for airway collapse on induction. This is especially true for large anterior mediastinal tumors. In such cases, these patients should undergo an incisional biopsy under awake and local anesthesia in an upright sitting position to obtain a diagnosis and determine an individualized treatment strategy. General anesthesia should be avoided as it could lead to catastrophic consequences due to tumor compression of the airway and result in inability to ventilate or oxygenate. In case of loss of airway secondary to airway compression by the tumor, a bail-out salvage maneuver would be to expeditiously sit the patient upright and utilize a rigid bronchoscope to establish airway access. Due to the emergent nature of such a dreadful crisis, timely cannulation for extracorporeal membrane oxygenation (ECMO) may not be feasible.

Additional anesthesia considerations include use of a double lumen endotracheal tube for thoracoscopic approaches to allow for single lung ventilation and collapse of a lung to improve visualization. Single lumen endotracheal intubation is also acceptable as long as intrathoracic carbon dioxide insufflation is maintained, and low tidal volumes are used. We recommend the use of an arterial line for continuous hemodynamic monitoring, and at least one large bore intravenous catheter in the lower extremities to be used for resuscitation, especially in case of potential significant hemorrhage secondary to injury of the superior vena cava or innominate veins. A central venous catheter and a urinary bladder catheter are usually unnecessary. The patient should have a type and screen with crossmatch for two units of packed red blood cells, and a sternal saw must be readily available on the field for an expeditious sternotomy if required.

Surgical approaches for thymectomy

Historically, thymectomy has been performed using open approaches, including trans-sternal, trans-cervical, or a combination of both techniques (maximal thymectomy). Advances in minimally invasive surgery (MIS) have revolutionized the approach to thymectomy. Beyond the standard open techniques, the modern-day thoracic surgeon has a range of options in the surgical treatment of thymus pathologies. Multiple reasons influence the choice of approach to thymectomy, including tumor factors (i.e., tumor size, laterality), patient factors (i.e., prior surgeries, body mass index or body mass index (BMI), narrow costal angle), and surgeon factors (i.e., experience with a specific technique during training, preference towards robotic surgery). Broadly, the approaches to thymectomy can be classified into two general categories, and further sub-classified according to operative technique:

(I) Open thymectomy:
  (i) Trans-sternal thymectomy
  (ii) Trans-cervical thymectomy
  (iii) Maximal thymectomy (trans-cervical + trans-sternal)

(II) Minimally invasive [video-assisted thoracoscopic surgery (VATS) or robot assisted]:
  (i) Trans-thoracic thoracoscopic (unilateral or bilateral)
  (ii) Subxiphoid thoracoscopic
    ❖ Uniportal
    ❖ Multiportal subcostal

Principles of surgery

Regardless of the surgical approach to thymectomy, adherence to certain surgical principles is a must to achieve optimal outcomes. The goal of surgery is to achieve a total thymectomy with complete resection of the thymoma, the thymus, and the surrounding pericardial fat with wide macroscopic margins and negative microscopic margins on histopathology (R0 resection). This decreases the risk of recurrence and removes any additional synchronous thymoma that may have not been detected preoperatively. During thymectomy, the bilateral pleural spaces are accessed and evaluated for metastatic implants, and the bilateral phrenic nerves are identified. The phrenic nerves act as the lateral extent of the total thymectomy, and care is taken to preserve these. To reduce the risk of iatrogenic phrenic nerve injury, we advise gentle tissue handling close to the phrenic nerve. In case of tumor invasion into a phrenic nerve, this can be resected with impunity if, preoperatively, the ipsilateral diaphragm was evaluated and found to be paralyzed. In case of a functional diaphragm with an involved phrenic nerve, the nerve may be resected provided the patient has adequate pulmonary reserve. It is noted, however, that in cases of MG, respiratory decompensation may be provoked by resecting only one nerve. In cases of tumor involvement of the bilateral phrenic nerves, one phrenic nerve must be preserved to prevent bilateral diaphragmatic paralysis and postoperative respiratory failure. To ensure complete resection, the thymus along with the pericardial fat, are mobilized and resected between the bilateral phrenic nerves. In addition, the final specimen should include the superior thymic poles, which are identified and traced into the neck, as well as the pericardial fatty tissue all the way inferior onto the diaphragm. Depending on the extent of the thymoma and its invasion into adjacent organs, additional *en-bloc* resection of involved structures (with possible reconstruction) is necessary to achieve R0 resection. Unilateral involvement of the innominate vein does not require reconstruction, however, bilateral involvement or invasion into the superior vena cava would require vascular reconstruction of only one of the innominate veins, depending on surgeon's preference. If there is unresectable disease (such as bilateral phrenic nerve invasion), this can be debulked as safely as possible and clips can be left in place at the resection margins as markers for future radiation therapy. Gentle and careful tissue handling technique is of utmost importance to avoid violation of the tumor capsule, the occurrence of which would substantially increase the risk of tumor spillage and future local recurrence. For minimally invasive approaches, prior to extraction, the specimen should be placed in an extraction bag to prevent tumor spillage and drop metastases.

Iatrogenic phrenic nerve injury will lead to ipsilateral diaphragmatic paralysis. This can be addressed with diaphragmatic plication ideally at the time of the index operation, however, diaphragmatic plication could also be performed at a later time. The left recurrent laryngeal nerve is also at risk during surgical dissection in the area between the aortic arch and left main pulmonary artery, and injury of this will lead to ipsilateral vocal cord paralysis.

Trans-sternal thymectomy

Alfred Blalock in 1939 performed the first thymectomy via partial sternotomy in a patient with MG with thymoma (24). He then published a series of planned thymectomies for non-thymomatous MG in 1941 (25). The trans-sternal approach to thymectomy allows for excellent access and visualization of the thymus and mediastinal fat (19,20). This technique involves a standard median sternotomy incision from the manubrial jugular notch down to the xiphoid process. The incision can be extended cephalad to the neck, for a so called trans-cervical trans-sternal 'maximal' thymectomy, if necessary, to achieve complete thymic tissue resection. The trans-sternal approach is ideal for large tumors or in cases where bulky *en-bloc* resections and/or vascular reconstruction are anticipated. The advantage of this technique is excellent exposure at the expense of a large incision and its sequelae, including increased postoperative pain. Despite the excellent exposure of the trans-sternal approach, visualization of the distal left phrenic nerve remains a challenge. As minimally invasive techniques and technology continue to advance, it is likely the utilization of open thymectomy approaches will further decrease. Nevertheless, it is important to note that, oftentimes, open surgical approach may provide improved quality of resection of thymic tumors (including thymic carcinoid tumors).

Trans-cervical thymectomy

In 1969, Kirschner and colleagues reported trans-cervical resection for MG in 21 patients (26). They described a short uneventful postoperative course by avoiding the morbidity of sternotomy. Contraindications included large, inaccessible thymomas and low-lying preexisting tracheostomy. Cooper *et al.* showed that the transcervical approach could provide complete thymectomy with minimum morbidity in MG patients (27).

Trans-cervical approach to thymectomy (27) has the advantage of avoiding trans-thoracic incisions, less pain, decreased need for chest tubes, and shorter hospital stay (28,29). This technique is suited for thymectomy in the setting of non-thymomatous MG and has previously been shown to have comparable results to trans-sternal thymectomy (30).

Trans-cervical thymectomy may be performed with or without video assistance. Following single lumen endotracheal anesthesia, ensuring proper positioning is critical to the success of the operation. The patient's arms are tucked to the sides, the head is positioned at the top edge of the operating table, and the neck is extended using an inflatable balloon behind the shoulders. An approximately 5 cm transverse curvilinear cervical incision is created about 2 cm cephalad to the sternal notch and subplatysmal flaps are created up to the level of the thyroid cartilage and down to the level of the sternal notch. The cervical horns of the thymus are then dissected and divided between ligatures, taking care to ligate branches from the inferior thyroid vessels. The left cervical thymic horn is usually dissected and divided first as it typically extends higher in the neck. The thymus is then retracted anteriorly, and dissection then continues inferiorly and around the left innominate vein, taking care to ligate and divide thymic venous tributaries. A Cooper retractor is then used to retract the sternum anteriorly, and the inflatable bag is deflated. The substernal plane anterior to the thymus is further developed, followed by mobilization of the thymus from the pleurae laterally and the pericardium inferiorly and posteriorly. This part of the dissection is usually performed bluntly, with occasional use of an energy device. Care is taken to identify and protect the bilateral phrenic nerves, although proper visualization is extremely difficult, which is one of the main drawbacks of this approach.

Minimally invasive thoracoscopic thymectomy

Thoracoscopic thymectomy was introduced in 1992 with a goal to reduce the morbidity of sternotomy, improve patient acceptance and provide superior cosmesis (31,32). Minimally invasive thymectomy encompasses conventional trans-thoracic VATS, sub-xiphoid VATS, and robot-assisted thoracoscopic surgery (RATS) for both trans-thoracic and sub-xiphoid approaches. Minimally invasive techniques have been found to have improved postoperative outcomes along with less blood loss, faster recovery, lower complications, and shorter hospital stays compared to open approaches (12,19,20). Minimally invasive approaches had the best performance in MG and small thymomas without vascular invasion (12), long-term oncological outcomes were also equivalent in comparison (19,20). One study analyzed MIS with thymomas and found all resections to be complete with negative margins (12). Additionally, there was no significant difference in operative times. With robotic-assisted approaches there is improved precision, dexterity,

ergonomics, and visualization of bilateral phrenic nerves (19,20,33). Concern has been reported in the literature regarding VATS having an increased risk of malignant pleural spread due to manipulation and possible tearing of the tumor with spillage tumor cells, however this remains controversial (17). The main concern with thoracoscopic thymectomy is an incomplete or compromised surgical excision given limited studies and availability to observe long-term postoperative outcomes (19,20). The most frequently reported difficulties that arise during minimally invasive thymectomy occur when the tumor is bulky, advanced, or invading into the chest wall or vessels (33). Despite these concerns, the quality of resection remains mostly unchanged compared to the historically done open approach, and this technique has shown to have lower morbidity and mortality (12,15,17,34). This further supports the idea of MIS becoming the preferred approach for thymectomy (17).

Both conventional thoracoscopic and robot-assisted approaches have been extensively adopted, though for both the surgical principles remain the same. Both unilateral and bilateral thoracoscopic approaches have been described. The patient is positioned in the lateral decubitus position. Lung isolation with a double-lumen endotracheal tube or bronchial blocker is usually required for visualization of the surgical field. Most commonly, three ports are placed in the chest, either right or left depending on the surgeon's preference. The thymus is dissected off the sternum and pericardium, followed by separating it off the phrenic nerve with sharp dissection. The horns are excised mostly from the right side. For the unilateral approach, the left-sided dissection is completed by pulling the thymus to the right. For the bilateral approach, additional ports are placed on the contralateral side to visualize the contralateral phrenic nerve and complete the dissection. There is no consensus on the preferred laterality for unilateral thoracoscopic thymectomy (35-37).

Subxiphoid subcostal thoracoscopic thymectomy

Kido *et al.* first described the subxiphoid subcostal thoracoscopic thymectomy technique in 1999 (38). They used a single transverse incision over the xiphoid, followed by xiphoid resection, and placed a sternal lifting system for exposure. The thymectomy was then performed via this single incision. As the technique evolved over the following decades, additional subcostal trans-thoracic ports were introduced to aid with better visualization. This technique allows for supine positioning, avoids lung isolation and its risks, and provides optimal bilateral phrenic nerve visualization. Uniportal access for subxiphoid thoracoscopic thymectomy has been described (39). At the University of Minnesota, we have adopted the conventional multi-port subxiphoid subcostal thoracoscopic approach for all thymectomies.

The patient is positioned supine with both arms abducted and a footboard to enable steep reverse Trendelenburg. We use a single lumen endotracheal tube and low tidal volume ventilation without positive end-expiratory pressure. We place a 15 mm subxiphoid port for initial access and advance it into the right pleural space. We then place two additional 5 mm subcostal ports approximately 5–8 cm away in each hemithorax. Under thoracoscopic visualization, we place additional 5 mm lateral subcostal ports in the anterior axillary lines bilaterally. The subcostal ports are inserted above the diaphragmatic insertion on the costal margin to reduce the risk of diaphragmatic hernia.

The dissection of the thymus is then performed keeping in line with standard surgical principles as previously described. The advantages of this approach are that the camera is freely moved between ports to help with careful visualization of both phrenic nerves (*Figure 1*). Subxiphoid thymectomy also provides excellent access to the most cephalad extent of the thymic horns. We also believe that this technique allows for superior evaluation of the thoracic cavity for tumor implants, and therefore improved resection and disease staging. Variations of this approach include a sternal retractor to increase the anteroposterior diameter of the mediastinum, which permits an increased working space. This is especially helpful in male patients with high BMI, in which cases visualization is more challenging.

Conclusions

The evolution of surgical techniques in the modern era allows for a wide array of surgical approaches to be safely used in the treatment of thymic pathologies. Complete resection of all thymic tissue remains the goal to achieve optimal results, while minimizing iatrogenic injury. The best surgical approach is the one that suits the individual patient's needs after careful evaluation of the patient's pathology and an assessment of the surgeon's preference.

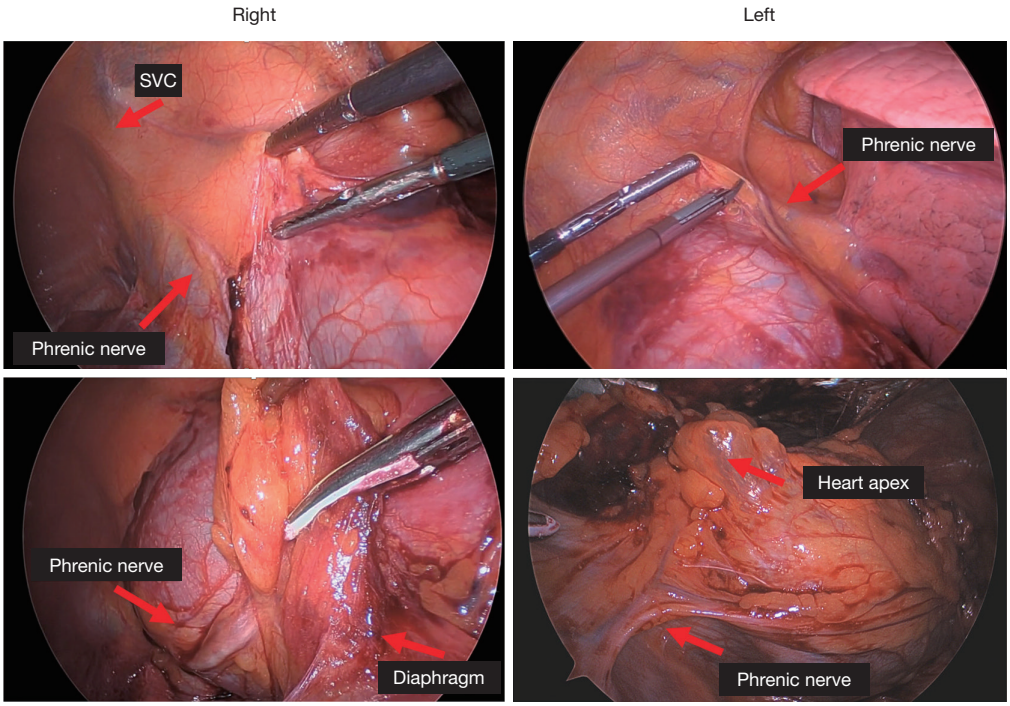

Figure 1 Intraoperative picture during subxiphoid subcostal thoracoscopic thymectomy. The right phrenic nerve is visualized lateral to the SVC. The entire thymic tissue is excised between the right and left phrenic nerves, adhering to the basic operative principles. SVC, superior vena cava.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-24-38/rc

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Review Article

Mediastinal lymph node cryobiopsy guided by endobronchial ultrasound: a comprehensive review of methods and outcomes

Shiwani Kamath, Abdullah Jahangir, Salim Daouk, Houssein A. Youness

Interventional Pulmonary Program, Section of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Oklahoma Health Sciences Center and The Oklahoma City VA Health Care System, Oklahoma City, OK, USA

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Correspondence to: Houssein A. Youness, MD, FCCP. Interventional Pulmonary Program, Section of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Oklahoma Health Sciences Center and The Oklahoma City VA Health Care System, 800 Stanton L Young Blvd, Suite 8400, Oklahoma City, OK 73104, USA. Email: houssein-youness@ouhsc.edu.

Abstract: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the preferred initial method to diagnose and stage non-small cell lung cancer. EBUS-guided transbronchial cryobiopsy (EBUS-TBC) is a newer technique with the potential to address the limitations of EBUS-TBNA. Only a few studies have explored this technique and compared its diagnostic yield to that of EBUS-TBNA. This review aims to summarize the existing literature and provide insights into the optimal yield and technique for performing EBUS-TBC. A comprehensive search of the PubMed database was conducted for studies published up to May 2024 related to EBUS-TBC. The PICO framework (Participants, Intervention, Comparison, and Outcome) was used to evaluate the diagnostic yield, techniques employed, and associated complications. Eleven studies involving 857 patients were identified. In these trials, EBUS-TBC was performed after EBUS-TBNA at the same lymph node station. Techniques varied among bronchoscopists, with most procedures conducted under moderate sedation. The TBNA needle sizes ranged from 19G to 22G. Three trials used a needle knife for the initial mucosal incision, while others utilized the initial puncture site for cryoprobe insertion. Nine studies employed a 1.1-mm Erbe cryoprobe, with a median freezing time of 4 seconds (range, 3–7 seconds). The overall diagnostic yield of EBUS-TBC was 91.9%, compared to 76.6% for EBUS-TBNA alone, with EBUS-TBC yielding larger specimens. Mild bleeding was the most common complication reported. The addition of EBUS-TBC to EBUS-TBNA enhances the diagnostic yield without significantly increasing complications. The larger biopsy samples obtained can be particularly valuable for next-generation sequencing in lung cancer and for improving diagnostic accuracy in benign diseases and rare malignancies like lymphoma.

Keywords: Cryobiopsy; lymphadenopathy; mediastinum

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Introduction

The evaluation and diagnosis of mediastinal and hilar lymphadenopathy have evolved over the last several decades. Options for diagnosis offered are surgical methods, cervical or anterior mediastinoscopy (Chamberlain procedure), and less invasive methods, endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS). EBUS-guided transbronchial needle aspiration (EBUS-TBNA) is the preferred diagnostic modality for non-small cell lung cancer (NSCLC) and has been adopted as an initial diagnostic method per newer guidelines (1).

Depending on the underlying etiology, TBNA has varying

results. For NSCLC, EBUS-TBNA has a sensitivity of 92.3% and a specificity of 100% (2). Molecular diagnostics, such as histological subtyping and genomic profiling in NSCLC, is possible in 86.5% of samples with EBUS-TBNA (3). In sarcoidosis, the diagnostic accuracy of EBUS-TBNA is 79% (4). The sensitivity of EBUS-TBNA in lymphoma is 66.2% (5).

Bronchoscopic cryobiopsy is a reasonably new development, gaining popularity in recent years. It uses compressed gas to cool surrounding tissue, known as the Joule-Thomson effect (6). The standard technique is to apply the probe adjacent to the target tissue, allow a temperature drop between −35 and −50 ℃ for several seconds to ensure adequate adhesion to surrounding tissues, and then remove the probe with attached tissue (7).

EBUS-guided transbronchial cryobiopsy (EBUS-TBC) for lymph node biopsy was first published in 2021. Compared to a yield by EBUS-TNBA of 53.2% for benign lesions and 25.0% for non-lung cancer tumors, the EBUS-TBC yield was 80.9% and 91.7%, respectively (8). The results suggest an advantage of cryobiopsy, especially in non-cancerous lymphadenopathy, and could potentially avoid the need for cervical mediastinoscopy. This paper serves to assess the literature regarding cryobiopsy, technique, as well as yield, outcome, and risk.

Methods

Literature search

A thorough literature search was conducted on PubMed, Cochrane, and Embase using the terms “EBUS cryobiopsy”, “transbronchial lymph node cryobiopsy”, and “lymph node cryobiopsy”.

The search was not limited to any region as long as an English translation was available. Articles from conferences were also included. There was no age filter applied for the patient population. Our cut-off date for this search was May 1, 2024.

Eligible studies included those in which bronchoscopic cryobiopsy probe was used to sample mediastinal or hilar lymph nodes and those that reported a diagnostic yield and safety outcomes.

Study selection

Two independent authors screened studies (A.J., S.K.) in regard to the title and abstract. Potential articles obtained from this initial review were then evaluated again by the full text by the same reviewers. Two authors individually assessed studies for bias utilizing the Quality Assessment Data Abstraction and Synthesis-2 (QUADAS-2). Studies were assessed in regard to patient selection, index test, reference standard, flow and timing. The reviewers then calculated the risk of bias and applicability concerns in each previously mentioned category as low, high, or unclear (*Table 1*).

Data extraction and analysis

Data extraction was performed utilizing pre-specified tables of baseline characteristics, the diagnostic yield of cryobiopsy, needle size, number of cryo-biopsies performed, cooling time, wall incision techniques, and complications.

Results

The literature search yielded 45 articles. After excluding ten duplicates, 35 articles were selected based on their titles and abstracts. After this evaluation, 16 studies were found to be possibly useful for our review. Subsequently, the full texts of these articles were reviewed. Five articles were then excluded, the reason listed are as follows: review papers (n=1), articles without relevant outcomes (n=2), and abstracts and case reports (n=2) (*Figure 1*). A total of 11 studies were included in the final review (*Table 1*) (8-18).

Reported technique

The procedure for performing lymph node cryobiopsy

Highlight box

Key findings

- The addition of endobronchial ultrasound-guided transbronchial cryobiopsy (EBUS-TBC) to endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) increased diagnostic yield without significantly increasing complications.

What is known and what is new?

- EBUS-TBNA is preferred for non-small cell lung cancer.
- The overall yield of EBUS-TBC was 91.9% compared to 76.6% for EBUS-TBNA alone. Mild bleeding was the most common complication.

What is the implication, and what should change now?

- EBUS-TBC provides a higher diagnostic yield and larger biopsy samples, which are especially valuable for next-generation sequencing in lung cancer and for improving diagnostic accuracy in benign diseases and rare malignancies such as lymphoma.

Table 1 Studies looking at the yield of TBC

Author, year of publication	Design	No.	Risk of bias/ concern for applicability	Intervention	Wall incision	Sedation	Passes	Cooling time (s)
Zhang, 2021 (8)	RCT	197	Low/low	Alternating passes with TBNA 22G/21G and cryo 1.1	High-frequency needle knife	Moderate	TBNA 4 passes with or without 3 cryo passes	7
Cheng, 2024 (9)	RCT	155	Low/low	TBNA 22G/21G with forceps *vs*. TBNA with cryo 1.1	High-frequency needle knife	Moderate	TBNA 4 passes followed by 3 forceps or 1 cryo	7
Fan, 2023 (10)	RCT	271	Low/low	4 TBNA followed by one cryo 1.1	High-frequency needle knife	Moderate	TBNA 4 passes with or without 3 cryo passes	7
Poletti, 2024 (11)	Observational	48	Low/low	22G TBNA followed by cryo 1.1	Needle puncture site	General	TBNA followed by 1 cryo	6
Genova, 2022 (12)	Prospective	5	High/low	19G TBNA followed by cryo 1.1	Needle puncture site	Moderate	3 TBNA followed by cryo 2 passes	4
Gershman, 2022 (13)	Prospective	27	Low/low	22G TBNA followed by cryo 1.1/1.7	Needle puncture site or YAG laser	Moderate	2–4 TBNA followed by cryo 2–4 passes	3–4
Gonuguntla, 2021 (14)	Prospective	4	High/low	22/21/19G TBNA followed by cryo 1.1	Needle puncture site	General	TBNA followed by cryo 1–2 passes	3
Ariza-Prota, 2022 (15)	Prospective	4	High/low	22G TBNA followed by cryo 1.1	Needle puncture site	Moderate	4 TBNA followed by cryo 3 passes	3
Ariza-Prota, 2023 (16)	Prospective	50	High/low	22G TBNA followed by cryo 1.1	Needle puncture site	Moderate	TBNA followed by cryo 3 passes	4
Salcedo, 2023 (17)	Case series	50	Low/high	22G TBNA followed by cryo 1.1	Needle puncture site	Moderate	2 TBNA followed by cryo average of 4 passes	4
Maturu, 2024 (18)	Prospective	46	Low/low	19G TBNA followed by cryo 1.1	Needle Puncture site	Moderate	3 TBNA passes, and if ROSE negative cryo with 4 passes	5–6

G, gauge; RCT, randomized controlled trial; ROSE, rapid on-site evaluation; TBNA, transbronchial needle aspiration; TBC, transbronchial cryobiopsy; YAG, yttrium aluminum garnet laser.

varies among bronchoscopists. Nine studies reported procedures performed under moderate sedation, and two reported using general anesthesia for the performed procedures. Only one study utilized a rigid tracheoscope for intubation for the procedure (11). After a surveillance bronchoscopy and lymph node identified by EBUS, almost all studies performed a TBNA to create a puncture site for the cryoprobes to enter the mediastinal space (*Figure 2*). Needle gauge size varied; most studies used 22G, but 19G and 21G were also used. Cheng *et al.* also used forceps with TBNA to create an incisional track (9). Two studies used a high-frequency needle knife to make a small incision adjacent to the target before probe placement. The knife was then removed and replaced with a probe (8,10).

Erbe offers three sizes of single-use, flexible cryoprobes—1.1, 1.7, and 2.4 mm (19,20). All studies were performed with a cryoprobe size of 1.1 mm, except for one by Gershman *et al.*, who also used the 1.7-mm probe (13). The probe was advanced through the working channel into the lesion under direct visualization and further guided by real-time ultrasound imaging. Optimal location was left to the discretion of the proceduralists, who generally avoided areas with abundant blood flow or massive necrosis. After placing the cryoprobe, it was activated to cool down with nitrous oxide. Six studies froze tissue for 3 to 4 seconds (12-17), two studies for 5 to 6 seconds (11,18), and the

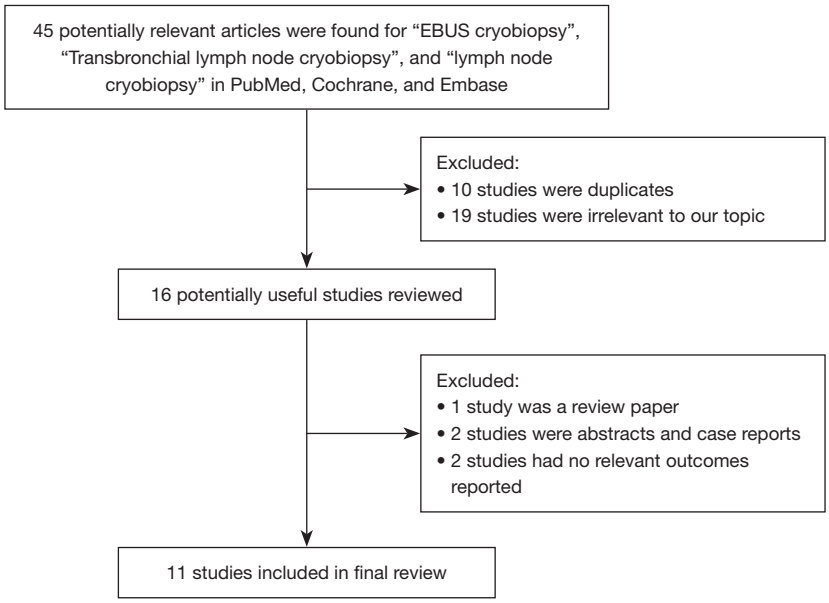

Figure 1 Flowchart of the search process for the review related to EBUS cryobiopsy of hilar and mediastinal lymph nodes. EBUS, endobronchial ultrasound.

remaining studies froze tissue for 7 seconds (8-10).

In all studies, the operator removed the bronchoscope and cryoprobe with attached frozen biopsy *en-bloc* from the airway. Since the sample from cryobiopsy is significantly larger than the working channel of the bronchoscope, it cannot be extracted through the channel. Samples were retrieved in saline and immediately placed in formalin. Rapid on-site evaluation (ROSE) was not routinely used. Compared to TBNA, cryobiopsy delivered larger biopsy sizes (0.46–0.47 *vs.* 0.18–0.20 mm) (16). Cheng *et al.* obtained cryobiopsy samples of 8.1 mm^2 compared to forceps biopsy sizes of 2.1 mm^2 (9).

The overall procedural time varied among studies, but performing cryobiopsy took additional time. Velasco-Albendea *et al.* and Ariza-Prota *et al.* reported 10 minutes to obtain a cryobiopsy in addition to the time taken to perform EBUS (16,21). Fan *et al.* reported a difference in total time between EBUS-TBNA alone or with the addition of EBUS-TBC as 17.0 *vs.* 22.3 minutes (10). Zhang and colleagues reported the difference between performing EBUS-TBNA and EBUS-TBC as 2 minutes (8). Oikonomidou found it took 20–30 minutes to perform EBUS-TBNA but 30–40 minutes to perform EBUS-TBC (22). However, lymph node cryobiopsy took less time than lymph node forceps biopsy (1.7 *vs.* 3.3 minutes) (9).

Indications & contraindications

Any lymph node traditionally accessed through the bronchial tree is amenable to cryobiopsy (i.e., stations 2, 4, 7, 10 & 11). All patients needed to meet the criteria for bronchoscopy and EBUS. Mediastinal cysts or abscesses are usually excluded. The standard size of lymph nodes biopsied was ≥1 cm. Fan *et al.* did not specify size limitation, but the average diameter of lymph nodes biopsied via cryobiopsy was 2.0 cm (10).

In some studies, the surrounding vascularity was measured via the Doppler-mode blood flow via ultrasound and categorized per Nakajima *et al.*'s grading system: grade 0: no blood flow or minimal flow; grade I: a few vessels directed toward the center of the lesion; grade II: punctiform or rod-shaped flow signals or vessels found as a long strip of a curve; and grade III: rich flow with at least five vessels with different diameters and a twist or helical-flow signal (23). For lesions that were grade III, indicating significant blood supply, another node or site was selected to limit complications (10).

Complications

The most common complication was bleeding. Bleeding was classified per a previously published scale by Ernst *et al.*

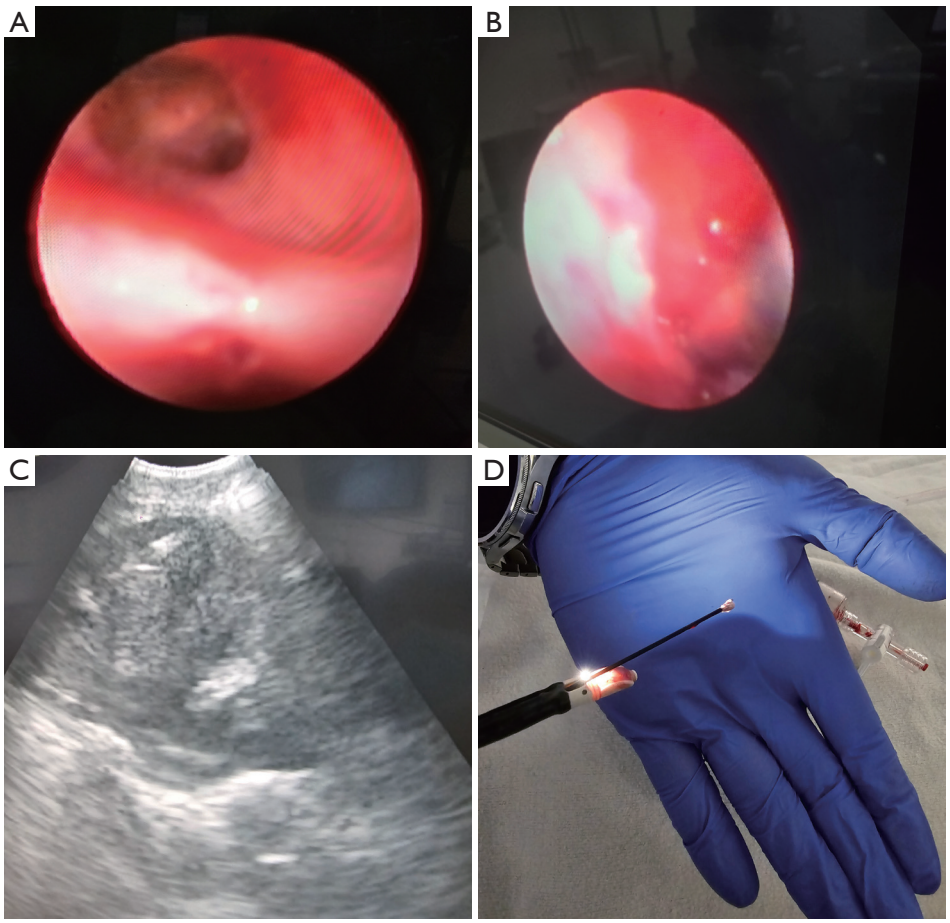

Figure 2 Execution of EBUS-guided lymph node cryobiopsy. (A) Bronchial view of mediastinal space puncture-site access after TBNA. (B) Cryoprobe entering the puncture site under direct visualization. (C) Direct visualization via EBUS of cryoprobe entering lymph node. (D) Frozen tissue surrounding the cryoprobe tip after the probe is removed *en-bloc*. These images are published with the patient's consent. EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration.

and Yarmus *et al.* as follows: grade 0: no suctioning required; grade 1: bleeding requiring suctioning and wedging for 2 minutes or less; grade 2: bleeding requiring wedging for at least 3 minutes; grade 3: bleeding requiring instillation of epinephrine or iced saline; and grade 4: bleeding requiring hemodynamic support including transfusion of blood products, selective mainstem intubation, bronchial blocker placement, hospital admission, or other surgical intervention (24,25). Most studies reported minor bleeding (grade 0–1). Pneumothorax or pneumomediastinum was another reported complication noted on post-procedural radiography. These occurred at a rate of <2% and resolved without further intervention. Salcedo Lobera *et al.* reported that out of the 50 patients involved in their study, two patients experienced hypoxemia requiring an increase in oxygen supplementation, and 1 developed a vocal cord hematoma; however, all patients were discharged home on the same day as the procedure (17). None of the above complications were statistically significant compared to the control group, suggesting that cryobiopsy offers no significant additional procedural risk.

Yield

Overall yield

Several recent studies have compared the efficacy of EBUS-TBC *vs.* EBUS-TBNA (*Table 1*).

The overall mean and median yield of EBUS-TBC reported in the studies was 91.9% and 92.4%

Table 2 Overall yield for EBUS-TBC and EBUS-TBNA

Author, year	Cryobiopsy			TBNA		
	Population	Yield	Percentage	Population	Yield	Percentage
Cheng, 2024 (9)	154	141	91.6	154	118	76.6
Zhang, 2021 (8)	194	178	91.8	194	155	79.9
Fan, 2023 (10)	136	126	92.6	135	109	80.7
Poletti, 2024 (11)	48	46	95.8	48	26	54.2
Genova, 2022 (12)	5	3	60.0	5	4	80.0
Gershman, 2022 (13)	24	20	83.3	24	21	87.5
Gonuguntla, 2021 (14)	4	4	100.0	4	3	75.0
Ariza-Prota, 2022 (15)	4	4	100.0	4	3	75.0
Ariza-Prota, 2023 (16)	50	48	96.0	50	41	82.0
Salcedo, 2023 (17)	50	45	90.0	50	32	64.0

EBUS-TBC, endobronchial ultrasound-guided transbronchial cryobiopsy; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Table 3 Yield in benign pathology

Study	No. of patients with benign pathology	Cryobiopsy yield (%)	TBNA yield (%)
Cheng, 2024 (9)	47	78.7	59.6
Zhang, 2021 (8)	47	80.9	53.2
Fan, 2023 (10)	48	94	66.7
Gonuguntla, 2021 (14)	2	100	100
Ariza-Prota, 2023 (16)	12	100	60

TBNA, transbronchial needle aspiration.

compared to 76.6% and 78.2% or EBUS-TBNA alone with a corresponding range of 60–100% and 54–87.5% respectively (*Table 2*). One study looked at the yield of cryobiopsy when the ROSE of the EBUS-TBNA was indeterminate or nondiagnostic. Cryobiopsy achieved diagnosis in 33 of 46 cases compared to 19 of 46 patients with EBUS-TBNA alone (18).

Benign etiologies

For benign etiologies of lymphadenopathy, including sarcoidosis and tuberculosis, cryobiopsy reportedly had a higher yield in several studies (8-10,14,16). The overall median reported yield for benign lymphadenopathy diagnosis with EBUS-TBC was 94% compared to 60% with EBUS-TBNA alone with a range of 78.7–100% and 53.2–100% respectively (*Table 3*).

Malignant etiologies

The overall yield for detection of malignant lesions overall was reportedly 94.36% with EBUS-TBC and 86.85% with EBUS-TBNA. The diagnostic yield for common lung tumors was 95.21% with EBUS-TBC and 92.67% with EBUS-TBNA (8-12,14-17). EBUS-TBC outperformed EBUS-TBNA significantly in detection of uncommon tumors in the lung with reported yield of 90.14% with EBUS-TBC and 57.75% with EBUS-TBNA (8-12).

Lymphoma

Cheng *et al.* reported successful lymphoma diagnosis in 13 out of 15 cases using EBUS-TBC compared to 11 with forceps biopsy (9). Fan *et al.* included ten patients with lymphoma with EBUS-TBC, providing the diagnosis in 8 patients compared to 5 with EBUS-TBNA (10). Zhang reported an 88% (7/8) yield for lymphoma *vs.* 13% for TBNA alone (8). Ariza-Prota *et al.* reported 4 cases of lymphoma in their cohort, and all of them were diagnosed with EBUS-TBC (16). In the study by Maturu *et al.*, EBUS-TBC was able to identify two additional cases of lymphoma after negative ROSE with EBUS-TBNA (18).

Sarcoidosis

Cheng *et al.* reported a yield of 92% for sarcoidosis with EBUS-TBC (11/12) compared to 75% with EBUS-TBNA alone (9). Zhang *et al.* reported a 100% yield (15/15) for sarcoidosis with EBUS-TBC compared to 66% with TBNA (8). Fan *et al.* included 16 patients in their cohort diagnosed with sarcoidosis with an EBUS-TBC yield of 100% compared to 75% for TBNA (10). Poletti *et al.* reported 13 patients diagnosed with sarcoidosis with EBUS-TBC compared to 11 with EBUS-TBNA (11). Gershman *et al.* and Gonuguntla *et al.* reported 11 and 1 case of sarcoidosis testing positive both with EBUS-TBC and EBUS-TBNA (13,14). Maturu *et al.* reported 2 cases of sarcoidosis detected with EBUS-TBC that were not detected with TBNA (18). Only one study by Salcedo Lobera *et al.* reported a higher detection rate with EBUS-TBNA (4 cases) than EBUS-TBC (2,17).

Molecular testing

Three studies compared the ability to run molecular testing on the available specimens. Zhang *et al.* reported that 93% of cryo samples were adequate for molecular testing compared to 73% for TBNA (8). Fan *et al.* reported 97% of samples with cryo as adequate for molecular and programmed death-ligand (PD-L) testing compared to 79% with TBNA (10). Ariza-Prota *et al.* and Genova *et al.* reported all samples as adequate for molecular testing (12,16).

Discussion

Cryobiopsy of pulmonary tissue is an established technique to obtain a pathological diagnosis in interstitial lung disease. It has also been validated in tumor debulking, foreign body extraction, and endobronchial tissue diagnosis. Cryobiopsy for mediastinal and hilar lymphadenopathy has gained popularity over the past few years. The need for targeted treatments, including immunotherapy and chemotherapy in the case of NSCLC, requires a significant amount of tissue to obtain molecular and genetic profiles of the tumors. Similarly, in the case of benign lung diseases, a greater sample size might be needed to delineate the underlying architecture of the lymph node, making EBUS-TBC an attractive option for diagnosis.

Multiple methods of introducing the cryoprobe have been described, and practice varies across providers, but generally, the results have been excellent, and complication rates remain low. Initial studies (8-10) used the high-frequency knife to create a hole in the airway wall to access the lymph node. This technique may require expertise. However, most recent studies have reported using the hole already created by the TBNA to introduce the cryoprobe, which might have an easier learning curve for experienced EBUS operators.

Cryobiopsy outperformed TBNA in most studies for diagnosis of sarcoidosis and pneumoconiosis. One study (17) reported significantly higher cases of proliferative histiocytosis diagnosed with the use of cryobiopsy. It also performed remarkably well in diagnosing benign etiologies of lymphadenopathy compared to TBNA alone, making it an attractive option when such a diagnosis is clinically suspected.

Cryobiopsy also outperformed EBUS-TBNA for detection of malignant lesions, regardless of if they were common or uncommon lung tumors. Cryobiopsy also obtained sufficient tissue for molecular testing as overall sample adequacy was reportedly around 95%. Similarly, the detection and tumor characterization rates for lymphoma were significantly higher in the cryobiopsy group, with an overall yield of over 90%. This marks a remarkable improvement on TBNA, which in literature has a reported sensitivity of around 77% (26). This increase in yield might be explained by the need for histologic analysis rather than cytologic analysis needed for the characterization of lymphomas, which might not be possible with samples from TBNA.

Since the end-date of our literature review, Romero *et al.* and Chandragiri *et al.* have since published a comprehensive review of EBUS-TBC (27,28). However, these studies included case reports, which we did not include, and overall fewer randomized controlled trials. These studies, when read along ours, provide a broader literature review.

Limitations

One major limitation is the inconsistent lymph node size criteria used across studies. Most studies included in this review utilized a size threshold of greater than 1 cm for biopsies, which contrasts with the widely accepted clinical guidelines recommending biopsy for nodes larger than 0.5 cm in EBUS (29). This divergence introduces selection bias and limits the generalizability of the findings, especially for smaller lymph nodes that are frequently biopsied during standard EBUS procedures. The complication rate could

be higher when aiming at doing a cryobiopsy of a smaller lymph node.

The adequacy of next-generation sequencing in EBUS-TBNA may be underestimated in this review. Our article compared studies that did molecular testing in the same lymph node between EBUS-TBNA and EBUS-TBC. The largest one of them by Zhang *et al.* reported a difference of 93% *vs.* 73% for the ability to run molecular testing on EBUS-TBC *vs.* EBUS-TBNA respectively (8). The other two trials were of smaller number and included 5 or less patients. There was also no standardized definition for adequacy of molecular testing. This is in contrast to systematic reviews which report higher rates of adequacy (94.5% for EGFR and 94.9% for ALK mutations) by EBUS-TBNA (30).

Lastly, the financial implications of EBUS-TBC are not well reported. There were no mentions of cost analysis in the listed studies.

Conclusions

Overall, cryobiopsy is a safe procedure with excellent results that can be used as an adjunct to already practiced techniques. The benefit of preventing repeat procedures with better yield from the addition of EBUS-TBC might compensate for the additional procedural time required. There is a need for standardization of the procedure techniques and training structure. Large multi-center studies are needed to integrate cryobiopsy into algorithms for mediastinal node sampling.

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Footnote

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Review Article

Practical value of fluorodeoxyglucose positron emission tomography in treatment strategies for thymic epithelial tumors: implications for more specific use in routine clinical practice

Kazuo Nakagawa

Department of Thoracic Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan
Correspondence to: Kazuo Nakagawa, MD. Department of Thoracic Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. Email: kazuo_nakagawa@tmhp.jp.

Abstract: Many studies have demonstrated that 18-fluorine fluorodeoxyglucose positron emission tomography (FDG-PET) is useful for predicting the grade of malignancy of thymic epithelial tumors (TETs), and there is a close relationship between the maximum standardized uptake value (SUVmax) and tumor stage. However, more specific usage of FDG-PET for TETs has not been proposed, and the actual value of FDG-PET in routine clinical practice should be firmly clarified. In this review, following three cutoff values of SUVmax that may be helpful in determining treatment strategies in cases of anterior mediastinal masses, particularly presented as discrete and resectable lesions, are identified: (I) SUVmax of 7.5 as an indicator for pretreatment biopsy: differential diagnosis between TETs and mediastinal lymphoma (ML); (II) SUVmax of 4.2 as an indicator for a minimally invasive approach (MIA): differentiation of noninvasive TETs and invasive TETs; and (III) SUVmax of 5.9 as a reference value for the necessity of lymph node dissection (LND). There are still several challenges in using FDG-PET for routine clinical practice that need to be addressed, such as variations between instruments and institutions, leading to lower reproducibility. Harmonization methods should be applied to make clinical practice more uniform. Due to the rarity of these diseases, multi-institutional studies are warranted.

Keywords: Thymic epithelial tumor (TET); fluorodeoxyglucose positron emission tomography (FDG-PET); mediastinal lymphoma (ML); minimally invasive approach (MIA); lymph node dissection (LND)

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Introduction

18-fluorine fluorodeoxyglucose positron emission tomography (FDG-PET) is crucial for evaluating malignant tumors before determining treatment strategies. For thymic epithelial tumors (TETs), numerous studies have examined the importance of FDG-PET (1-5). To date, they have demonstrated that FDG-PET is useful for predicting the grade of malignancy in TETs, and in particular, that there is a significant difference in FDG uptake between thymoma and thymic carcinoma (TC) (3-5). In addition, several studies have investigated the relationship between tumor stage and the maximum standardized uptake value (SUVmax) and demonstrated that SUVmax increases in more advanced-stage tumors (5,6). On the other hand, in the initial management of anterior mediastinal lesions, for a tumor that is considered to be resectable, surgical resection is recommended without a biopsy to confirm the histological diagnosis before surgery (7). In this situation, the role of FDG-PET before treatment remains unclear. However, in routine clinical practice, even with such simplified strategies, there are several important points that thoracic surgeons should keep in mind. First, even in resectable tumors, particularly tumors that manifest as a well-defined anterior mediastinal mass in the thymic bed, mediastinal lymphoma (ML) should be ruled out (8,9). Second, surgical approaches are an essential part of surgical procedures (10).

To date, median sternotomy has been considered to be the standard approach. On the other hand, in the National Comprehensive Cancer Network (NCCN) guidelines, minimally invasive procedures may be considered for clinical stages I–II if all oncologic goals can be met as in standard procedures (7). Hence, accurate prediction of invasion is the most important issue in determining surgical approaches. Third, FDG-PET is essential for evaluating lymph node (LN) status when establishing treatment strategies. In TETs, the clinical significance of LN metastasis has not been fully investigated, and the necessity of LN dissection during surgery is still controversial (11).

Thus, simplified strategies contain some important points, and FDG-PET can be a potentially useful tool for this situation. This review investigates the significance of FDG-PET in terms of these three issues.

Articles written in English were researched on PubMed. The retrieval terms used were "thymic epithelial tumors" combined with "FDG-PET" and "malignant lymphoma" OR "stage" OR "lymph node metastasis". The inclusion criteria were clinical studies with comprehensive pathological results detailing histological subtype and stage, emphasizing the differences in SUVmax between TETs and MLs, as well as between early-stage TETs and advanced-stage TETs.

Necessity of differentiation of TETs from MLs, particularly in discrete and resectable masses

Thymic tumors are the most common primary tumors of the anterior mediastinum, mainly including TETs, lymphomas, and germ cell tumors (GCTs) (12,13). TETs and MLs can account for more than 50% of all anterior mediastinal tumors, and are the two most common anterior mediastinal tumors (14,15). For different types of anterior mediastinal tumors, the treatment options are also totally different. Most TETs are usually treated with surgery, while surgery should be avoided for MLs, and the systemic treatments for advanced TETs and MLs are also different. Since resection is recommended without confirmation of the histological diagnosis before surgery for a resectable tumor (7), a few total thymectomies are inevitably performed for patients with a tumor other than TETs. Indeed, Kent *et al.* reported the prevalence of a "nontherapeutic" thymectomy in the Nationwide Inpatient Sample. They demonstrated that 363 (27.8%) of 1,306 total thymectomies were nontherapeutic. Among them, 46 (3.76%) were performed for patients with MLs (16). In another report, among 160 thymectomies, 38 (23.8%) were performed for patients with MLs (17). Thus, to avoid futile thymectomies, even for a resectable anterior mass, it is important to differentiate TETs from MLs. However, the differential diagnosis between TETs and MLs using FDG-PET has still not yet been fully evaluated. To date, several studies have investigated the significance of FDG-PET for differentiating TETs from MLs (8,18-22).

Zhu *et al.* retrospectively investigated primary thymic neoplasms that had been pathologically diagnosed as TETs or MLs on the basis of surgical findings or core needle biopsy specimens, and immunohistochemistry testing to assess whether FDG-PET image features combined with clinical information can distinguish TETs from MLs for the first time. The cutoff value of SUVmax with the best diagnostic performance was 12.3 with an area under the curve (AUC) of 0.764 (sensitivity: 70.4%, specificity: 70.8%) (18). At present, five studies have investigated the differences in SUVmax between TETs and MLs (8,18-21). The details are shown in *Table 1*. Patients with ML were significantly younger than patients with TET. Regarding histological subtypes of MLs, diffuse large B-cell lymphoma and classic Hodgkin lymphoma are common. SUVmax in MLs tended to be higher than that in TETs. The cutoff values of SUVmax to differentiate TETs form MLs are around 10. Most of the studies included both resectable and unresectable tumors. For an unresectable lesion, in routine clinical practice, histological confirmation should always be performed. In this situation, differentiation between TETs and MLs with FDG-PET seems to be less valuable. Of these five studies, only one study by Byrd *et al.* examined a total of 48 patients with resectable thymoma and 29 of those with ML that manifested as a discrete and resectable lesion. The median SUVmax values of thymoma and ML differed dramatically: 4.35 versus 18.00 ($P<0.001$). SUVmax values less than 7.50 and 12.85 were associated with thymoma with 85.4% sensitivity and 100.0% specificity, and 100.0% sensitivity and 79.3% specificity, respectively. MLs are likely with an SUVmax value greater than 12.85. They concluded that tumors with an SUVmax value greater than 7.50 should be biopsied to rule out MLs (8).

Thus, although several optimal cutoff values of SUVmax in the tumor for differentiating TETs from MLs have been reported, many factors contribute to the range of a cutoff value including tumor size, histological subtypes of TETs and MLs, and the extent of the tumor. The threshold SUVmax value that separates TETs from MLs needs to be further evaluated, particularly for a discrete and resectable

Table 1 Studies on SUVmax and cutoff value between thymic epithelial tumors with mediastinal lymphomas

Authors	Inclusion criteria	No. of patients	Gender	Age (years, mean ± SD)	Histologic subtype	SUVmax	Cutoff value of SUVmax	AUC, sensitivity, specificity
Zhu *et al.* [2020] (18)	TETs and MLs	TETs: n=65	TETs: male, 61.5%; female, 38.5%	TETs: 54.2±15.2	TETs: thymoma, n=26; TC, n=31; NET, n=8	TETs: 10.6±6.2	12.3	0.764, 70.4%, 70.8%
		MLs: n=71	MLs: male, 31.0%; female, 69.0%	MLs: 30.3±14.4	MLs: DLBL, n=30; HL, n=26; TLL, n=9; others, n=9	MLs: 16.6±6.4		
Wang *et al.* [2022] (19)	TETs (surgery: n=28, biopsy alone: n=52) and MLs (biopsy alone: n=93)	TETs: n=80	TETs: male, 61.0%; female, 39.0%	TETs: 50.8±14.8	TETs: thymoma, n=28; TC, n=44; NET: n=8	TETs: 7.2±4.3	10.5	0.845, 74.2%, 85.0%
		MLs: n=93	MLs: male, 56.0%; female, 44.0%	MLs: 30.3±14.6	MLs: DLBL, n=37; HL, n=31; TLL, n=23; others, n=2	MLs: 15.5±7.6		
Byrd *et al.* [2023] (8)	Thymomas and MLs that manifested as a discrete, resectable lesion	TETs: n=48	TETs: male, 35.4%; female, 64.6%	55.0	TETs: thymoma, n=48	TETs: 4.4	7.50[a] or 12.85[b]	[†]NR, 85.4%, 100.0% or [‡]NR, 100.0%, 79.3%
		MLs: n=29	MLs: male, 44.8%; female, 55.2%		MLs: DLBL, n=20; HL, n=7; others, n=2	MLs: 18.0		
Zhou *et al.* [2024] (20)	Invasive TETs and MLs	TETs: n=61	TETs: male, 54.1%; female, 45.9%	TETs: 55.8±11.4	TETs: thymoma, n=33; TC, n=28	TETs: 7.6±4.6	9.7	0.841, 77.8%, 81.9%
		MLs: n=72	MLs: male, 55.5%; female, 44.5%	MLs: 28.9±10.4	MLs: DLBL, n=28; HL, n=16; TLL, n=11; others, n=10	MLs: 15.7±8.2		
Yan *et al.* [2024] (21)	TETs and MLs (surgery: n=125, biopsy alone: n=105)	TETs: n=186	TETs: male, 53.8%; female, 46.2%	TETs: 50.4±15.6	TETs: thymoma, n=82; TC, n=84; NET, n=20	Low-risk thymoma: 5.6±2.3, high-risk thymoma: 7.2±2.7, TC: 12.4±5.5, NET: 12.8±7.4	12.0	0.890, NR, NR (accuracy: 78.3%)
		MLs: n=44	MLs: male, 52.3%; female, 47.7%	MLs: 32.0±12.7	MLs: DLBL, n=25; HL, n=10; TLL: n=9	MLs: 21.6±8.6		

Values are presented as the median value for the study by Byrd *et al.*, or as the mean ± SD for other studies. The superscripts [†] and [‡] indicate the AUC, sensitivity, and specificity for each cutoff value of SUVmax for [a] and [b], respectively. AUC, area under the curve; DLBL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; MLs, mediastinal lymphomas; NET, neuroendocrine tumor; NR, not reported; SD, standard deviation; SUVmax, maximum standardized uptake value; TC, thymic carcinoma; TETs, thymic epithelial tumors; TLL, T-lymphoblastic lymphoma.

lesion. A multi-institutional study should be considered.

Usefulness for determining a surgical approach: standard approach or minimally invasive approach (MIA)

Surgical approaches for TET include a trans-sternal approach and MIAs, such as video-assisted thoracic surgery (VATS) and robot-assisted thoracic surgery (RATS) (10). The choice of approach is important for achieving an appropriate surgical view for complete tumor resection. As mentioned above, in the NCCN guidelines, minimally invasive procedures may be considered for clinical stages I–II if all oncologic goals can be met as in standard procedures (7). Accordingly, in preoperative evaluations, predicting the presence or absence of invasion to the neighboring structures in patients with TETs is important. Several studies have investigated the relationship between tumor stage and SUVmax, and have demonstrated that SUVmax is higher in more advanced-stage tumors. Matsumoto *et al.* reported a significantly higher SUVmax for Masaoka-Koga stage IV compared to stages I–II as well as for larger tumors (≥60 mm) (23). Conversely, in the study by Fukumoto *et al.*, the SUVmax of stages III–IV thymomas showed a higher trend toward stages I–II thymomas (24). However, the optimal cutoff values between noninvasive tumors and invasive tumors have not been fully investigated. To date, only a few studies have investigated the difference in SUVmax between noninvasive disease (stages I–II) and invasive disease (stages III–IV). Ito *et al.* analyzed the association between FDG uptake and Masaoka-Koga stage or tumour-node-metastasis (TNM) stage. They found a significant difference in SUVmax between Masaoka-Koga stages III–IV and stages I–II, and identified an optimal cutoff value of 5.4 (sensitivity: 85.0%, specificity: 80.0%). The SUVmax in TETs according to T factors of the TNM classification was 4.45±2.06 in T1a, 4.9±0 in T1b, 7.12±2.69 in T2, 8.31±2.57 in T3, and 9.79±7.48 in T4, and T3 TETs had significantly higher SUVmax than T1a TETs (P<0.01). They also reported a significant difference in SUVmax between TNM stages III–IV and TNM stages I–II, and identified an optimal cut-off value of 5.6 (sensitivity: 89.0%, specificity: 78.0%) (25). Akamine *et al.* retrospectively analyzed patients who exhibited TNM clinical stage I TETs with lesion size <5 cm as determined by computed tomography (MIA-candidate TETs). FDG-uptake in the tumor tended to gradually increase from TNM pathological stage I to IV. The ROC analysis demonstrated that the AUC was 0.820 [95% confidence interval (CI): 0.646–0.919], and the best cutoff value of SUVmax to differentiate the diagnosis of upstaged and pathological stage I patients was 4.2 (sensitivity: 88.9%, specificity: 72.5%) (26).

Thus, preoperative FDG-PET could be useful for the differentiation of invasive TETs and noninvasive TETs. These findings provide valuable information for thoracic surgeons to help them select the appropriate approach for patients with TETs. In routine clinical practice, regardless of FDG-PET findings, MIA is usually adopted for such tumors. However, information on the possibility of invasion to surrounding structures could help thoracic surgeons to determine the surgical approach and prepare for conversion to an open approach before surgery. In addition, it is also important that some information on the possibility of conversion from MIA to an open approach or combined resection of neighboring structures can be provided to patients before surgery. Thoracic surgeons should keep in mind the possibility of more aggressive tumors with the necessity of combined resections of neighboring structures, particularly in high FDG-uptake tumors.

Role of FDG-PET in the decision-making regarding the necessity of LN dissection

One of the most critical roles of FDG-PET when dealing with malignant tumors is evaluating the presence or absence of LN metastasis. In particular, FDG-PET is essential in assessing LN status in several cancers. Regarding the status of LN metastasis in TETs, a study by Fang *et al.* demonstrated that LN involvement rates were 1.5% in thymomas, 17.6% in TCs, and 27.7% in neuroendocrine thymic tumors (27). These findings are identical to those of several other studies (28,29). Since thymoma is the most common entity among TETs, an LN involvement is rare in TETs. Due to this rarity, the usefulness of FDG-PET for evaluating LN status and the necessity of LN dissection in TETs has not been thoroughly investigated. On the other hand, several studies have demonstrated the risk factors for LN metastasis in TETs, and these findings can give valuable suggestions on the role of FDG-PET for LN evaluation in TETs (29,30).

A previous prospective landmark study by Fang *et al.* found three independent risk factors for LN metastasis in TETs, including histology (type B3 thymoma, TC, and thymic neuroendocrine tumor), pathological T category (T3 and T4), and dissection of N2 lesion (29). Another study by Wang *et al.* on the factors that predicted LN metastasis

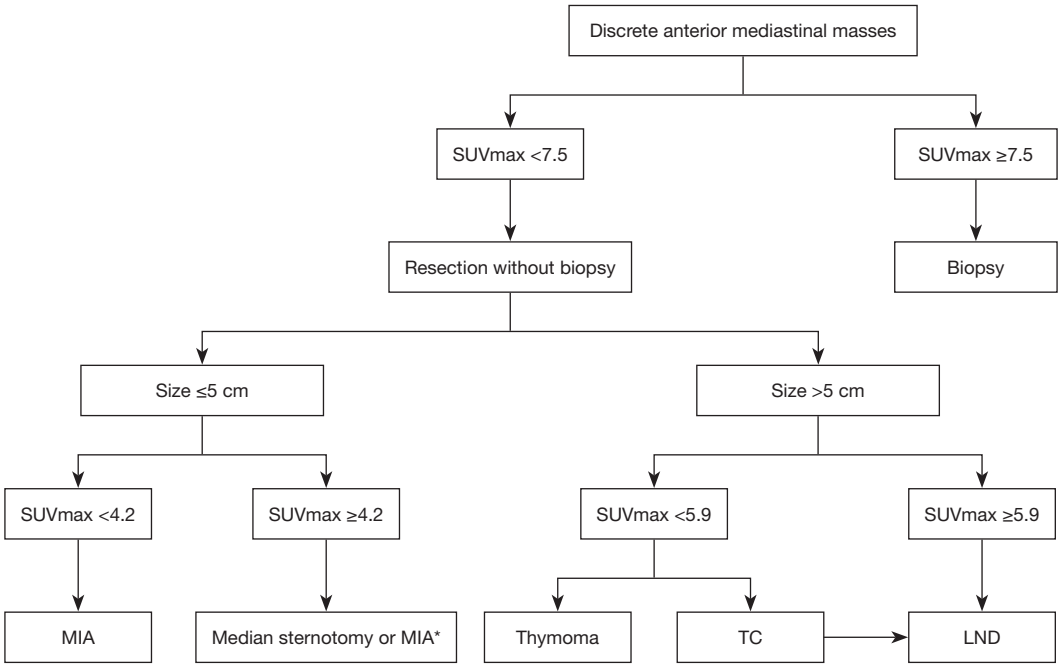

Figure 1 Treatment strategies for discrete anterior mediastinal masses in non-myasthenic patients based on the NCCN guidelines combined with SUVmax in the tumor. *, if performed in specialized centers by surgeons with experience in MIA techniques. LND, lymph node dissection; MIA, minimally invasive approach; NCCN, National Comprehensive Cancer Network; SUVmax, maximum standardized uptake value; TC, thymic carcinoma.

found that pathological T category (T3 and T4) and histology (TC) were significant factors (30). Their model showed good accuracy for predicting LN metastasis with a C-statistic of 0.807 (95% CI: 0.773–0.841), indicating that the nomogram had a good discrimination ability for estimating the status of LN in TETs. Furthermore, the prediction model (AUC =0.807) performed better than predictors of the T category (AUC =0.597, P<0.001) or histology (AUC =0.790, P=0.047) alone. Thus, the risk factors for LN metastasis in TETs include pathological T factors and high-grade histology, particularly TC. Accordingly, FDG-PET might become an important modality in determining the necessity of LN dissection, since it can accurately predict these factors to some extent.

To date, only one study by Akamine *et al.* has addressed the potential use of FDG-PET for the determination of LN dissection for TETs (31). They revealed that LN metastasis was found only in patients with a tumor SUVmax of more than 5.9. Furthermore, none of the patients with SUVmax <5.9 had LN metastasis, LN recurrence, but they had a good prognosis, even in a pathologically advanced stage. They suggested that LN dissection could be omitted in patients with cN0 tumors with low FDG-uptake, even if the tumor is TC. Furthermore, in their previous study, after thymomectomy (resection of tumor without total thymectomy) without extensive LN dissection, no LN recurrence was observed in c-stage I TC <5 cm in size with PET-negative LN, suggesting that LN dissection can be omitted in limited patients (26).

At present, although the necessity of LN dissection in TETs remains controversial, based on the International Thymic Malignancy Interest Group recommendation (32), Hwang *et al.* demonstrated that necessity of LN dissection including paratracheal node for stage II or higher thymic malignancies (28). More reasonable strategies for LN dissection in patients with TET could be established by combining several clinicopathological factors and SUVmax.

Treatment strategies for discrete anterior mediastinal masses

Figure 1 shows a flowchart for treatment strategies based on the NCCN guidelines combined with three cutoff values of SUVmax reported in several articles. First, an SUVmax

of 4.2 is used as a cutoff value between pathological stage I TETs and more advanced-stage TETs in patients with clinical stage I TETs smaller than 5 cm (26). Second, use of an SUVmax cutoff of 5.9 is based on the findings by Akamine *et al.* (31) that none of the patients with SUVmax <5.9 had LN metastasis, LN recurrence, but had a good prognosis, even in a pathologically advanced stage. Finally, an SUVmax of less than 7.5 identified thymoma with 100% specificity; this suggests that tumors with SUVmax less than 7.5 may be resected without biopsy (8). These strategies are merely a proposal to apply existing FDG-PET findings to routine clinical practice, and cannot be generalized to every institution. For example, regarding approaches, if performed in specialized centers by surgeons with experience in MIA techniques, MIA can be selected even for patients with a tumor that is appropriate for a standard procedure in the NCCN guidelines. Furthermore, as mentioned in the NCCN guidelines, biopsy of a possible thymoma should avoid a transpleural approach because of the substantial risk of converting a stage I thymoma to a stage IV thymoma by spreading tumor within the pleural space (7). Accordingly, the cutoff value of SUVmax for biopsy of discrete lesions may need to be set to a higher value, as recommended by Giles and Cassivi (9). To apply an optimal cutoff value of SUVmax widely in routine clinical practice, there are still many issues with FDG-PET for TETs. One of the most critical issues is the reproducibility and predictive performance of radiomic features derived from different centers and scanners. Quantitative values in FDG-PET depend on technical, biological, and physical factors. In addition, such variability may have a significant impact on clinical outcomes. Harmonization methods should be adapted for FDG-PET in TETs in the future (33).

Conclusions

Anterior mediastinal tumors consist of various tumors, and treatment strategies vary even in resectable lesions. In addition, surgical procedures also include many components. For establishing more precise treatment strategies and performing surgery more safely and effectively, FDG-PET could play an essential role in patients with an anterior mediastinal mass, particularly those that present as a discrete and resectable lesion.

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Footnote

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Review Article

The role of positron emission tomography in mediastinal mass

Audrey C. Pendleton, Joshua R. Sonett

Division of Thoracic Surgery, Columbia University Medical Center, New York, NY, USA

Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Audrey C. Pendleton, MD. Assistant Professor of Surgery, Division of Thoracic Surgery, Columbia University Medical Center, 161 Fort Washington Avenue, 3rd Floor, New York, NY 10032, USA. Email: acp2118@cumc.columbia.edu.

Abstract: Mediastinal masses are a common finding in patients and can represent a diagnostic challenge for thoracic surgeons. The differential diagnosis for these masses is broad and ranges from benign solid or cystic lesions to aggressive cancers. They can present with vague symptoms, but these masses are often found incidentally in asymptomatic people. Patients with mediastinal masses should be evaluated by a multidisciplinary team of specialists, including thoracic surgeons. Determining the etiology of the mass is essential since this heavily determines the management and prognosis. The work up involves clinical evaluation, laboratory work and always involves imaging, but deciding which imaging modality will offer the most information about the lesions and guide management is not always clear. The most common imaging studies for mediastinal masses are computed tomography (CT) scans, magnetic resonance imaging (MRI), and positron emission tomography (PET) scans. The role of PET scans in the work up of these masses is not well-established, but these scans have been shown to be especially useful in certain circumstances and can help guide further work up and decision making. This review article evaluates how and when PET scans can be used to guide work up and management in a variety of mediastinal masses.

Keywords: Positron emission tomography (PET); lymphoma; thymoma; mediastinal mass

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Introduction

The differential diagnosis for mediastinal masses is broad and ranges from benign entities to aggressive malignancies and everything in between. When working them up, a multi-faceted approach is taken in order to narrow the differential and help delineate the type of mass and the stage, which is imperative for decision making. Chest imaging plays a significant part in the assessment of mediastinal masses and often helps determine subsequent steps in diagnosis and management. Positron emission tomography (PET) scans are commonly used in clinically staging malignant tumors. The role of PET scans in the work up and management of mediastinal masses has been controversial and inconsistently utilized with little consensus in the literature about how best to apply it. In this paper, we address the use of PET scans in mediastinal masses and how it influences diagnostic work up and management.

Clinical review

Patients presenting with mediastinal masses can present a diagnostic challenge to thoracic surgeons. They can be found due to work up for symptoms but are often found incidentally on imaging. The location of the mass often helps to narrow the differential diagnosis. The mediastinum is bordered by the pleura laterally on both sides and the thoracic inlet and diaphragm superiorly and inferiorly, respectively. It is further divided into anterior, middle and posterior compartments. About half of all mediastinal masses are anterior, and are comprised of thymic masses, lymphomas, germ cell tumors, or thyroid disease (1).

Middle mediastinal masses are typically benign cystic lesions and posterior ones are neurogenic tumors. The initial study is often a computed tomography (CT) scan of the chest, which can give some indication of the etiology, but often more detailed imaging is needed. PET scans are most useful in evaluating anterior masses (2), with some use in posterior masses (3), and less often used for middle mediastinal masses, which tend to be benign cystic lesions.

When evaluating a patient with an anterior mediastinal mass, determining its etiology is critical prior to treatment since the treatment algorithms are different depending on the diagnosis. For example, thymomas and thymic carcinomas are treated with resection, lymphoma with definitive chemotherapy, and germ cell tumors with chemotherapy followed by resection for residual disease. In the initial diagnostic work up, patient demographics, tumor characteristics, symptoms, lab work and imaging are used. Characteristic findings on lab work, such as elevated alpha fetal protein and beta human chorionic gonadotropin (HCG), especially in a man, can confirm a suspected non-seminomatous germ cell tumor. Certain characteristics on imaging can also help elucidate the etiology of the mass (4). Adjunctive imaging, such as magnetic resonance imaging (MRI) or PET, is often performed, with PET being used to help differentiate between benign and malignant disease and to monitor response to treatment (5). In a study looking at lymphoma patients, PET was found to be more accurate in assessing post-treatment response and excluding residual nodal disease (6).

Determining the difference between lymphoma and thymoma is not always clear, but it is crucial to planning treatment. PET scans have been shown to be useful in these settings. In a retrospective study, Byrd *et al.* evaluated patients with a diagnosis of lymphoma and thymoma and associated PET findings. They found a significant difference in the standardized uptake value (SUV) between lymphoma and thymoma, 18 *vs.* 4.35, respectively (P<0.001). In this study, an SUV less than 12.85 was associated with thymoma with a sensitivity of 100% and a positive predictive value of 89%. Furthermore, an SUV less than 7 had a 100% positive predictive value for diagnosing thymoma. The utility of differentiating between thymoma and lymphoma is significant given the risk of seeding the tract and upstaging thymoma with percutaneous biopsy and so is discouraged by the National Comprehensive Cancer Network (NCCN) when possible. Based on these findings, a mass deemed resectable should be removed surgically without a biopsy if the SUV is less than 7. If it is above 12.85, then lymphoma is a much more probable diagnosis, and a biopsy should be performed. For masses with SUV between 7 and 12.85, a biopsy should be performed in most cases, but with some consideration based on the appearance of the mass and where on the spectrum the SUV falls (7). If imaging largely favors lymphoma based on clinical presentation and imaging, such as bulky lymphadenopathy with a higher SUV, then we would pursue a biopsy, using the PET as a guide for where to biopsy in order to most efficiently yield a diagnosis.

In addition to aiding in narrowing down the differential, PET scans are key in clinical staging once a diagnosis of cancer is made, especially in lymphoma, thymic carcinoma, and germ cell tumors. In lymphoma, PET scans are much more accurate in determining lymphogenic spread to distant nodes than CT scan, with a sensitivity of 94% and a specificity of 100%. The PET is also key in providing targets of active disease for biopsy, essentially serving as a "map", especially when patients with suspected lymphoma have bulky heterogenous lymphadenopathy (8).

When managing a patient with an anterior mediastinal mass, it is helpful to ascertain which imaging studies will help in decision making, whether it be further diagnostic procedures or proceeding with surgical resection versus systemic therapy. PET scans are not routine "reflex tests" when working up anterior mediastinal tumors so it is important to know when they will contribute to management. Thymic neoplasms are best treated with surgical resection, but their size, location and staging are all determinants of how they are approached and if neoadjuvant treatment should be considered. Thymomas and thymic carcinomas have different features on imaging, with thymic carcinomas often being larger with irregular borders. PET scans can assist further in differentiating the two. Several studies have demonstrated that SUV cutoffs ranging between 4.6 and 5.6 can often reliably differentiate between thymoma and thymic carcinoma (9,10). In a prospective single series study, Terzi *et al.* evaluated patients with thymic neoplasms and used PET scans for each of them. They found a significant correlation between SUV and staging based on Masaoka staging system and the World Health Organization (WHO) classification, therefore suggesting that a PET scan can be used as a "liquid biopsy" in determining how advanced the malignancy is. This is useful since higher risk thymic neoplasms have a higher rate of local invasion and may benefit from neoadjuvant treatment (11). When thymomas recur, there is a higher risk of metastasis, known as "drop thymomas". When evaluating

a patient with a possible recurrence, a PET should be obtained to assess if any other abnormalities in the chest are drop thymomas by comparing their metabolic activity to the primary lesion on PET scan. Similarly, in thymic carcinomas, which have a higher rate of distant metastasis, a PET should be performed to ascertain this information, which guides treatment algorithms (12).

In addition to location and stage, the size of the suspected thymoma also helps determine what work up is appropriate, which may not include a PET scan. PET scans have little to no utility in isolated, small thymic masses that are consistent with early stage thymomas. In lesions ≤5 cm, a minimally invasive resection should be performed in good surgical candidates for both diagnostic and therapeutic intent. In larger lesions or ones that may involve adjacent structures, a sternotomy may be required for resection. In these cases, a PET should be done to elucidate the stage, identify targets for possible biopsy, assess for drop lesions and distant metastasis, and to help determine if neoadjuvant therapy should be given prior to considering resection.

The management of germ cell tumors is often a multi-pronged approach with a combination of chemotherapy and surgery depending on the response. PET scans are used not only to help in differentiating between benign and malignant germ cell tumors, but also in assessing response. This is especially helpful in seminomatous and non-seminomatous tumors, which are treated with up front chemotherapy, followed by surgery in certain cases. Non-seminomatous germ cell tumors are often diagnosed with elevated tumor markers, and these had been monitored to assess if surgical management was indicated after treatment. There has been a shift in this management, and now nonseminomatous germ cell tumors (NSGCTs) are often resected after chemotherapy when there is residual disease on post-treatment imaging, regardless of tumor marker levels (13). Therefore, PET scans should be obtained on initial diagnosis and be used to assess the response, the location and extent of residual disease after chemotherapy. This information aids in surgical planning and can determine if there is progression with distant metastasis, which would often deem the cancer unresectable or mandate further systemic therapy and reassessment. Seminomatous germ cell tumors had traditionally been managed non-operatively, but there has been a shift in treating them in a similar fashion to NSGCT, with systemic therapy, followed by surgery for residual resectable disease, so PET scans have become useful in this treatment algorithm as well (14). Therefore, once the patient has completed the systemic treatment, a PET scan should be performed to guide next steps and surgical planning.

When assessing a patient with an anterior mediastinal mass, there are numerous options for radiological technique. Most are first discovered with a CT scan. At this point, the surgeon needs to decide which additional imaging is most useful in determining the appropriate management. For small thymic lesions, an MRI is generally preferred over a PET because MRI can help distinguish between a cystic and solid mass as well as thymic hyperplasia. A PET in this situation would likely not contribute to the management. If the MRI shows a cystic lesion or thymic hyperplasia, then surveillance is a reasonable plan. If the MRI is consistent with a small thymoma, then we would recommend surgical resection without biopsy or PET. If, however, there is bulky lymphadenopathy, a large solid-appearing mass on CT, especially if it is involving nearby structures, or the workup is consistent with a germ cell tumor, then a PET is superior to MRI for clinical staging, planning biopsies and monitoring response to treatment (15). *Figure 1* illustrates an algorithm for how to approach the diagnostic work-up of mediastinal masses using imaging, biopsies and surgery.

There are few disadvantages to PET scans, the main one being their cost and, previously, their unavailability at many centers. As they have become more ubiquitous, they are now considered standard of care in many oncological workups, as seen in lung cancer. As such, their cost has decreased and in certain situations has been shown to be cost-effective when compared to other modes of imaging (16). Given its utility in guiding treatment algorithms and optimizing targets for biopsies, when used in the appropriate setting, the benefits outweigh the costs.

Conclusions

Given the broad differential of mediastinal masses and the significant variety in management depending on the pathology, the detailed imaging that PET scans can provide aids in embarking on the appropriate treatment in certain patients. Additionally, given the associated morbidity of biopsies in certain settings, using PET scans to better delineate these tumors can help clinicians avoid the morbidity associated with biopsies in some cases. In the case of germ cell tumors, with the increasing use of surgical resection after systemic therapy, PET scans have become essential in the management of these patients. While the utility of PET scans in mediastinal masses has not been standardized in all cases and the data are somewhat limited,

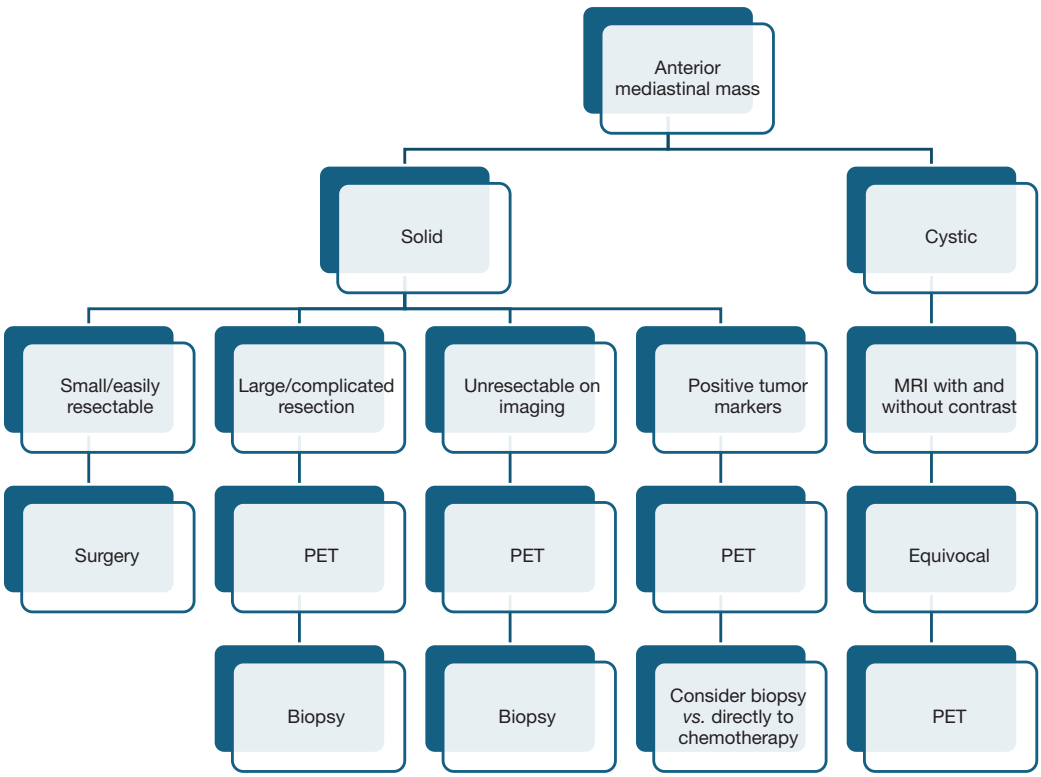

Figure 1 Algorithm for anterior mediastinal mass work up and management. MRI, magnetic resonance imaging; PET, positron emission tomography.

there is increasing work in the last decade to better guide how best to use them in the care of these patients.

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Footnote

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Review Article

Etiology, diagnosis, and management of descending necrotizing mediastinitis: a narrative review

Richard C. Chaulk[1], David Sahai[1], Leela Raj[1], Rahul Nayak[1,2]^

[1]Schulich School of Medicine, Western University, London, ON, Canada; [2]Division of Thoracic Surgery, Department of Surgery, London Health Sciences Centre, Victoria Hospital, London, ON, Canada

Contributions: (I) Conception and design: RC Chaulk, D Sahai, R Nayak; (II) Administrative support: R Nayak; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Rahul Nayak, MD, MSc. Schulich School of Medicine, Western University, London, ON, Canada; Division of Thoracic Surgery, Department of Surgery, London Health Sciences Centre, Victoria Hospital, E2-004, 800 Commissioner's Rd. E., London, ON N6A W9, Canada. Email: Rahul.nayak@lhsc.on.ca.

Background and Objective: Descending necrotizing mediastinitis (DNM) is a severe and life-threatening infection that originates from oropharyngeal or cervical infections and spreads downward into the mediastinum. Despite advancements in medical and surgical treatments, DNM remains a condition with high morbidity and mortality. This narrative review aims to summarize the etiology, diagnostic strategies, and management approaches for DNM, emphasizing the importance of a multidisciplinary approach.

Methods: A comprehensive literature search was conducted using PubMed/MEDLINE, Western University Libraries, and Google Scholar databases, without restriction on publication date. Articles were included if they discussed: (I) the etiology of mediastinitis, focusing on anatomy and pathogens; (II) the diagnosis of DNM; and (III) the treatment and surgical approach to mediastinitis.

Key Content and Findings: DNM is commonly caused by oropharyngeal infections that spread downward through normal anatomical pathways. Diagnosis is challenging due to the subtle and varied presentation of symptoms. Diagnosis is primarily made with contrast-enhanced CT scans of the neck and thorax, but a convincing history should prompt appropriate suspicion and concern. Management requires a multidisciplinary approach, including sepsis management particularly with broad-spectrum antibiotics and early surgical intervention for source control. The choice of surgical technique, whether transcervical, thoracotomy, or video-assisted thoracoscopic surgery (VATS), is crucial for effective drainage and reducing mortality.

Conclusions: DNM is a complex and critical condition that demands prompt recognition and aggressive treatment. The high mortality associated with DNM underscores the need for a multidisciplinary approach. Surgical drainage, tailored to the extent of the infection, and comprehensive post-operative care are essential for improving patient outcomes. Future research should focus on optimizing diagnostic criteria, refining surgical techniques, and exploring adjunct therapies to further reduce morbidity and mortality in DNM.

Keywords: Video-assisted thoracoscopic surgery (VATS); mediastinitis; necrotizing infection; mediastinal debridement

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^ ORCID: 0000-0003-1652-0417.

Introduction

Background

First described in 1938 by Dr. Pearse, descending necrotizing mediastinitis (DNM) was recognized for its complex and morbid nature, with Pearse quoting an 85% mortality rate without appropriate source control through aggressive surgical management (1). Since then, significant advancements in recognition, diagnosis, and treatment have considerably lowered the mortality associated with this condition. However, this condition remains a serious requiring aggressive management due to its relatively high complication and mortality rates. Mediastinitis, as outlined by Pearse in his landmark paper, may originate from various sources and have such divergent manifestations that the term "mediastinitis" alone offers little clinical clarity. Among the many types of inflammatory processes that can occur in the mediastinum, although relatively uncommon, DNM remains the most severe.

Rationale and knowledge gap

Despite recent advances in diagnosis and management of DNM, it remains a profoundly morbid condition with no clear consensus on the optimal surgical management. Within the literature, there exists no prospective studies with the amount of retrospective reporting remaining minimal and with ongoing dispute with respect to the optimal surgical management of this disease.

Objective

The goal of the present review is to address the potentially subtle and insidious presentation of DNM, present current approaches to diagnosis and discuss the multiply described techniques to surgical drainage. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-29/rc).

Methods

Our search of the literature was conducted between May 5 and June 10, 2024 and included the following databases: PubMed/MEDLINE, Western University Libraries, and Google Scholar databases. Literature used for this review was primarily obtained from PubMed/MEDLINE. A summary of our detailed search strategy is included in *Table 1*. Articles were screened and included if they either described: (I) the etiology of mediastinitis, including the important anatomy, patient profile, and implicating pathogens; (II) the diagnosis of DNM; and (III) the treatment of mediastinitis with particular focus on the variability in potential options for surgical drainage. Pertinent details of our search strategy are outlined in *Table 2*.

Content review

Etiology

Mediastinitis refers to any infectious or inflammatory process that occurs within the borders of the mediastinum affecting the connective tissue that fills the interpleural mediastinal space and surrounds the median thoracic organs (2). The process may range from a simple, non-suppurative process such as pericarditis or bronchitis to a severe diffuse purulent infection (1). Of the many types, DNM is the most severe requiring aggressive treatment and, even with advancements in treatments, this condition remains highly morbid. DNM refers to a clinical entity that, by definition, is preceded by an infection of an odontogenic or cervical origin that then spreads downwards to involve the mediastinum.

To understand the development of DNM, one must understand the basics of the anatomy of the cervical and thoracic fascial planes that facilitate the rapid and free spread of infection from the mouth and neck into the mediastinum. Essentially, there exists anatomic continuity between the cervical and mediastinal spaces that contain loose, poorly vascularized areolar tissue which lack immunologically active defense cells, thus serving as potential portals of entry facilitating spread of infection into the mediastinum (2).

Some authors argue that an absolute understanding of these pathways and anatomic planes is essential to fully comprehend the origin of the condition and thus dictate management (3). However, others have postulated that targeting these areas based on the suspected origin and propagation pathways for surgical management may result in incomplete drainage and insufficient source control (2). The main pathways that connect the two spaces allowing the spread of oropharyngeal infection into the mediastinum are the pre-tracheal, perivascular or perivisceral, and retropharyngeal spaces (1,3). Since the original description of the disease, the retropharyngeal space has been thought to be the most important route by which cervical infections progress into the mediastinum and is quoted to facilitate

Table 1 The search strategy summary

Items	Specification
Date of search	May 5 and June 10, 2024
Databases and other sources searched	PubMed/MEDLINE, Western University Libraries, and Google Scholar databases
Search terms used	"Mediastinitis", "etiology", "treatment", "retropharyngeal space", "microflora", "surgical approach", "VATS", "minimally-invasive surgery"
Timeframe	No restriction was placed on the date of publication of included articles
Inclusion criteria	No restrictions were placed on publication date or article type. Articles were included if they were written in English and met the following criteria: (I) the etiology of mediastinitis, including the important anatomy, patient profile, and implicating pathogens; (II) the diagnosis of DNM; and (III) the treatment of mediastinitis with particular focus on the variability in potential surgical drainage
Selection process	Selection process was conducted by R.C.C.
Any additional considerations, if applicable	A gray literature search of Google Scholar was also included to ensure thorough literature review

DNM, descending necrotizing mediastinitis.

Table 2 MEDLINE search strategy

Summary of MEDLINE search strategy:
("Mediastinitis" AND "Treatment")
("Descending necrotizing mediastinitis" AND "Approach" OR "technique")
("Descending necrotizing mediastinitis" AND "Etiology")
("Descending necrotizing mediastinitis" AND ("VATS" OR "minimally invasive")
("Descending necrotizing mediastinitis" AND "Tracheostomy")
("Descending necrotizing mediastinitis" AND "VATS" OR "Video-Assisted Thoracic Surgery")
("Descending necrotizing mediastinitis AND "antibiotic")

VATS, video-assisted thoracoscopic surgery.

70% of DNM (1).

The most commonly accepted origin of infection is from odontogenic sources. Often, second or third lower molar abscesses are implicated in deep neck infection (DNI) with subsequent progression to DNM (4). When the infection arises in this manner, the inciting event is known as Ludwig's angina and is a rare, but potentially severe infection that may lead to DNM (5). However, in a relatively large series reported by Ridder *et al.*, their most common source of DNM originated as pharyngeal infection. Less common sources of primary DNI that can cause DNM include peritonsillar abscess, epiglottitis, or lingual tonsillitis (2). There has been an association reported between radiation therapy to the pharyngeal area and the development of DNI, causing subsequent development of DNM (2).

The microbiology implicated in DNM is, not surprisingly, reflective of the normal microflora of the upper aerodigestive tract and become virulent only in certain conditions varying depending on the infectious origin. The most isolated aerobic bacteria tend to be various types of streptococcus species with streptococcus pyogenes being the most common; along with staphylococcus aureus (2). Anaerobic flora tend to consist of bacteroides, peptostreptococcus, and fusobacterium species (2). There have been reports of fungus, mainly candida, isolated in the setting of DNM but this is a rare entity and high suspicion for contamination should be considered unless the patient is otherwise immunocompromised (2). The polymicrobial nature of this infection in combination with the limited number of immune-competent cells found within the cervical mediastinum has been attributed to overall toxic nature of the disease (4).

Presentation

Prompt recognition of DNM can be challenging as the symptoms and signs of the infection present on a spectrum and are often subtle to non-existent until very late in the disease process. The classic symptoms often reported in the literature include chest pain, jugular venous distention, high fever, and crackling on palpation of the cervical area (2). However, the presence of these symptoms in isolation or together are rare with more common, and often

earlier, symptoms including sore throat, neck pain, headache, general fatigue, globus sensation, dysphagia or odynophagia (4). Nonetheless, in a patient with oropharyngeal infection and progression of symptoms, clinicians must remain highly suspicious of this disease process with a low threshold for further investigation.

Common comorbidities associated with DNM are generally those that result in reduced tissue level oxygenation. These include diabetes, heart failure, respiratory insufficiency, obesity, peripheral artery disease, or previous radiotherapy of the neck (2). Further, there has been a strong association between DNM and patients who are chronic, heavy smokers, and have a history of drug and/or alcohol abuse (6).

Diagnosis

The diagnostic criteria for DNM was first proposed by Estrera *et al.* in 1983 and were further refined by Wheatley *et al.* in 1990 (2,7). These criteria remain in use today and consist of (7):

(I) Clinical manifestations of severe cervical infection;
(II) Demonstration of characteristic radiographic features of mediastinitis;
(III) Documentation of necrotizing mediastinal infection at operation or post-mortem examination (or both);
(IV) Establishment of a relationship between oropharyngeal infection and the development of the necrotizing mediastinal process.

To satisfy criteria one and four, the most important step is a meticulous and thorough history and physical examination, which should include not only the presenting symptoms but also the delineation of the timeline and progression of these symptoms. Additionally, the diagnosis of odontogenic infection or DNI can be difficult and often requires consultation from otolaryngology or dentistry to examine the oral cavity and to directly visualize the larynx and pharynx using fibreoptic nasoendoscopy (4).

With respect to the radiographic features of mediastinitis, the main diagnostic tool accepted to make the diagnosis of mediastinitis (of any kind) is contrast-enhanced computed tomography (CT) scans of the neck and thorax. Common findings in keeping with DNM are a visible, organized fluid collection with or without gas formation, soft tissue thickening and enhancement with loss of the normal fat planes, reactive lymphadenopathy, septic vascular thrombosis, and can even include associated pleural or pericardial effusions (2). For patients with impaired renal function in whom there is significant concern for administration of intravenous contrast, or in children where there is concern for the impact of radiation, magnetic resonance imaging (MRI) is a suitable alternative.

The main classification system to describe DNM and potentially guide management was initially described by Endo *et al.* in 1999 and is based on the anatomical level of infectious involvement in the mediastinum (8). The classification system is relatively simple with type I infections limited to the area above the carina and type II specific to those that extend below (8). Type II is further classified into those involving the anterior lower mediastinum (IIA), and both the anterior and posterior lower mediastinum (IIB) (8). In 2021, Sugio *et al.* described a series of 225 patients and identified a previously undescribed subtype of DNM labelling it as type IIC (9). This group of patients were those with lower mediastinal disease only involving the posterior mediastinum (9).

Management

No definitive treatment for DNM has been clearly established. However, one theme that remains consistent in nearly all literature when managing DNM is a multidisciplinary approach involving thoracic surgery, otolaryngology, infectious disease, critical care, microbiology, and other teams, depending on the individual patient's needs and relevant comorbidities.

Once a diagnosis of DNM has been made, the fundamentals of sepsis management in the critically ill patient remain consistent: ensuring airway protection, adequate oxygenation, blood pressure support, antibiotics, and source control. However, between each of these broad management concepts, there exists nuance that depends on the etiology, disease course, patient profile, and severity.

Firstly, since DNM primarily originates from oropharyngeal infections leading to DNIs and subsequently progressing to DNM, there is a significant risk of airway compromise. Early consultation with the otolaryngology, thoracic surgery, and critical care teams is therefore crucial in the initial stages of management to secure the airway before proceeding with definitive source control. Generally, these patients benefit from early, rather than late, intubation to ensure appropriate oxygenation and to facilitate the impending surgical management required to achieve source control (4).

There exists debate surrounding the routine use of tracheostomy for patients with DNM. Some authors

believe that routine tracheostomy should be performed at the index operation for all patients with DNM due to the likelihood of prolonged necessity of invasive ventilation or potential for upper airway obstruction due to significant post-operative pharyngeal edema (10). However, some authors have called its routine use into question due to the risk of contamination of the tracheostomy site from the cervical wound needed for necessary drainage of DNI (11). Although no large series have specifically examined the routine use of tracheostomy in DNM management, the existing literature generally supports its liberal use in patients with significant medical comorbidities, particularly those with respiratory issues, who are expected to require prolonged mechanical ventilation in the intensive care unit (ICU) (2,4,11).

The optimal antibiotic choice in the management of DNM remains a difficult decision based on the polymicrobial nature of the infection and the necessity to cover aerobic and anaerobic bacteria. However, there is consensus regarding routine use of broad-spectrum intravenous antibiotics which are later tailored based on bacterial cultures obtained from surgical drainage (2,4,7,11). Common choices of empiric antibiotics include second and third generation cephalosporins with the addition of metronidazole or clindamycin for anaerobic coverage (2). An additional option is piperacillin-tazobactam to include coverage for both aerobic and anaerobic bacteria. Although in some reported series, there has been isolated fungal growth, there is no suggestion of routine use of anti-fungal medication in the empiric treatment of DNM (2).

One aspect of the management of DNM that remains universally accepted is that antibiotics alone are insufficient to control the disease necessitating the need for surgical source control. The approach to surgical management, however, varies depending on the origin and extent of disease and has also been a point of contention amongst surgeons treating this condition. The choice of surgical approach is crucial as the main cause of mortality in DNM has been quoted to be inadequate mediastinal drainage (12).

Surgical cervical drainage of DNI is a mandatory and non-controversial part of the management of DNM as inadequate cervical drainage will only continue to perpetuate the disease process. Following cervical surgical drainage, it is recommended to leave multiple, large surgical drains for ongoing source control with many authors opting to leave the wound open with daily packing and irrigation with anti-septic solution (2,4). This approach will also engage our nursing colleagues specializing in wound management as a part of the multi-disciplinary management of this complex disease.

The choice of approach to the thoracic mediastinum, however, remains a debated topic with options for thoracic drainage including trans-cervical, posterolateral thoracotomy, trans-sternal, sub-xiphoid and video-assisted thoracoscopic approaches.

Trans-cervical drainage of the mediastinum is a limited approach that provides access only to the superior mediastinum and may not permit adequate debridement and drainage of all purulent material (2,3,7,10-12). However, prior to 1990, nearly all cases of DNM were managed with transcervical drainage alone which likely contributed to its high mortality (13). Following this, in their retrospective review from 1997, Corsten *et al.* found a 47% rate of mortality with transcervical drainage alone and a 19% mortality rate with the addition of thoracic mediastinal drainage (14). However, a more recent and much larger retrospective series reported by Ridder *et al.* with 45 patients showed that the majority of their patients had disease limited to the upper mediastinum that were adequately drained with a trans-cervical mediastinal approach and a mortality rate of 11.1% (2).

Given this, however, multiple authors have condemned the isolated trans-cervical approach and routinely advocate for the addition of thoracic drainage, usually in the form of posterolateral thoracotomy (2). Ridder *et al.* argued that for disease confined to the superior mediastinum the additional surgical stress of posterolateral thoracotomy and intraoperative position changes may outweigh the risks of the potentially inadequate drainage from isolated trans-cervical drainage (2). The posterolateral thoracotomy offers access to the entire hemithorax, including all ipsilateral mediastinal structures and compartments allowing for adequate drainage (12). One potential disadvantage of posterolateral thoracotomy for drainage of the mediastinum is the lack of access to the contralateral hemithorax presenting challenges for patients with extensive, bilateral contamination (3). An early adaptation to this limitation, described by Ris *et al.*, is the clamshell incision (15). This approach offers a wide surgical field with access to bilateral hemithoraces for extensive exploration and drainage, however, it is extremely aggressive and has a significant impact on ventilation mechanics in already compromised patients (3). Additionally, there is added risk of phrenic nerve hyperextension, diaphragmatic paralysis, and carries risk of sternal osteomyelitis (similar to a sternotomy for mediastinal drainage) (3).

Another way to achieve access to bilateral pleural cavities, with the addition of significantly less surgical morbidity is a video-assisted thoracoscopic surgery (VATS) approach to mediastinal drainage. In a series of 11 patients with a 0% mortality rate, Wakahara *et al.* approached DNM with the traditional cervicotomy for drainage of DNI and a "mini-thoracotomy" to facilitate thoracoscopic assistance to achieve a minimally invasive and efficient drainage (11). In a larger systematic review, 28 patients underwent mediastinal drainage with a VATS approach with an 8% mortality rate (16).

Min *et al.* in their 2004 case series reported four cases using cervicotomy to obtain control of DNI and VATS for mediastinal drainage. Although no control group was present, they showed a 0% mortality and the only post-operative complications were persistent pleural effusion with no need for return to the operating room (7).

In a larger retrospective cohort study, Tanaka *et al.* compared patients who underwent mediastinal drainage via VATS or thoracotomy over a 4-year study period with the primary outcome defined as 90-day mortality and the adjusted risk difference between VATS and thoracotomy (17). They found that for patients with a poor performance status pre-operatively, there was tendency towards a VATS approach to mediastinal drainage whereas patients with infection extending to both the anterior and posterior lower mediastinum, there was a tendency to approach this via thoracotomy (17). With respect to their primary outcome, there was no statistically significant difference noted with 90-day mortality rates of 4.8% and 8.6% in the VATS and thoracotomy groups, respectively, and an adjusted risk difference of nearly zero (17). Additionally, there was no difference in post-operative outcomes including volume of blood loss, length of hospital stay in days, indwelling time of mediastinal drainage (days), rates or duration of mechanical ventilation (17).

Although there exists limited literature on the use of VATS in the drainage of DNM, preliminary studies show promising outcomes with similar outcomes without the associated morbidity of thoracotomy. However, in approaching DNM with minimally invasive approaches, one must remember that the disease progresses rapidly and infection can often extend beyond the region identified on pre-operative imaging and therefore, in cases when sufficient drainage is questioned using a VATS approach, thoracotomy should be performed (17).

Although reported in the literature, sub-xiphoid and parasternal or trans-sternal approaches to mediastinal drainage have resulted in less favorable outcomes.

In their systematic review including a total of 480 patients, Prado-Calleros *et al.* used their findings to propose a management decision making algorithm based on the Endo type of DNM (16). Multiple authors advocate for decision making based on the Endo classification with type I being drained with cervicotomy alone and type II having the addition of, usually, thoracotomy. However, it is imperative to recognize that no consensus has been reached among surgeons regarding the optimal surgical management, and the debate continues. Regardless of the surgeon's preference for drainage, it is crucial to consider the individual patient's ability to tolerate extensive surgery and weigh this against the risk of potentially inadequate drainage.

Regardless of the approach used in the surgical management of DNM, the most important aspect of the care provided to these patients is adequate and often, aggressive, source control. In the setting of cervicotomy, this often necessitates large, sometimes bilateral incisions to accommodate the finger of the surgeon to perform blunt dissection to explore the area and drain all recesses that harbor purulence. Further, the dissection of the mediastinum, if performed from the neck, should start at the base of the mandible and extend down to the area of the tracheal bifurcation. If the origin of infection is a result of a dental infection, all infected or necrotic must be removed to attain appropriate source control. In short, in the face of a life-threatening infection, the surgeon must perform careful, yet often radical, surgery to achieve adequate source control from the mouth, neck, or chest.

Despite extensive reporting of various techniques for sepsis control in the setting of DNM and the potential utility of classification systems in guiding management, the importance of an individualized, patient centered, approach to the surgical management of DNM cannot be understated. As outlined by Coltro *et al.*, all decisions made in the management of this complex condition should be individualized to the patient from empiric antibiotic choice, surgical approach, the choice of tracheostomy, and approaches to reconstruction, especially in the face of potential surgical complications (18). For example, in their presented case, they chose a median sternotomy and cervicotomy as their initial approach which allowed for appropriate sepsis control and stabilization of the patient, however, it was complicated by sternal dehiscence for which an individual decision was made for unilateral pectoralis major muscle flap was used for reconstruction to good effect (18).

Following surgical drainage of the mediastinum, patients generally require ongoing invasive ventilation in the ICU setting with an expected protracted hospital course. Some authors advocate for routine 48–72 hour post-operative contrast-enhanced CT scan of the neck and thorax to reassess the potential ongoing extent of disease and plan further management based on this (16). If there is expansion of the abscess or persistent localized abscess with worsening or ongoing septic shock, then re-exploration of the neck and/or mediastinum would be necessary (16). Another proposed approach is the liberal use of CT only if the patient's condition deteriorates with operative decision making planned around this repeat imaging (2). Nonetheless, consensus in the literature acknowledges the likelihood of these patients requiring repeat drainage procedures for adequate neck or mediastinal sepsis control with a generally liberal approach to re-operation if the patient's condition does not improve or significantly deteriorates.

As mentioned, these patients are expected to have a long, protracted course in ICU and hospital. While the multidisciplinary management of DNM is essential for obtaining appropriate infection control, post-operative multidisciplinary involvement is equally crucial. This includes the important addition of allied healthcare providers such as physiotherapy, occupational therapy, and speech-language pathology to address the expected post-operative deconditioning.

Limitations

In this study, several limitations warrant careful consideration of the findings. Primarily, the retrospective design of the included studies presents inherent challenges, as it may introduce biases that can influence the outcomes. These biases are often difficult to control or account for, potentially affecting the reliability of the results. Furthermore, the findings should be interpreted with caution, given that the scope of biases is extensive and beyond the authors' capacity to manage effectively. Therefore, while the results provide valuable insights, they should be viewed within this context, encouraging further research to validate and expand upon these conclusions.

Conclusions

DNM remains a formidable and potentially fatal condition despite advancements in medical and surgical interventions. The complexity of DNM, originating primarily from oropharyngeal infections, necessitates a high index of suspicion for timely diagnosis and management. The evolution from initial infection to mediastinitis underscores the importance of understanding the anatomical pathways involved. The consensus underscores the critical role of multidisciplinary management, emphasizing early and aggressive surgical intervention combined with broad-spectrum antibiotic therapy tailored to the polymicrobial nature of the infection.

Optimal management strategies continue to be debated, particularly concerning the surgical approach. While trans-cervical drainage remains a cornerstone for cervical infections, its adequacy for mediastinal involvement is often supplemented by thoracic drainage techniques such as posterolateral thoracotomy or minimally invasive methods like VATS. Each method carries distinct benefits and risks, underscoring the necessity for individualized patient assessment and tailored intervention strategies.

The main focus of future work in this disease should focus on the optimal surgical approach to drainage with special consideration given to minimally invasive techniques such as VATS. Despite the current challenges, continued advancements in understanding and managing this condition offer hope for reducing its high morbidity and mortality rates.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Case Report

Co-occurrence of thymoma and acute T-lymphoblastic leukemia/lymphoma: a case report and literature review

Nicholas Frazzette, Jeffrey Ordner, Navneet Narula, Andre L. Moreira, Christopher Y. Park, Nicholas D. Ward

Department of Pathology, NYU Langone Medical Center, New York, NY, USA

Contributions: (I) Conception and design: J Ordner, AL Moreira, ND Ward; (II) Administrative support: N Frazzette, AL Moreira, ND Ward; (III) Provision of study materials or patients: J Ordner, N Narula, AL Moreira, CY Park, ND Ward; (IV) Collection and assembly of data: N Frazzette, J Ordner, AL Moreira, ND Ward; (V) Data analysis and interpretation: N Frazzette, J Ordner, AL Moreira, ND Ward; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Nicholas D. Ward, MD. Department of Pathology, NYU Langone Medical Center, 550 1st Avenue, New York, NY 10016, USA. Email: Nicholas.Ward@nyulangone.org.

Background: A thymoma is a tumor originating from thymic epithelial cells variably associated with non-neoplastic lymphocytes. T-lymphoblastic leukemia/lymphoma (T-LBL) is thought to arise from precursor T-cells from bone marrow-derived hematopoietic stem cells that migrate to the thymus. While the association of secondary hematopoietic malignancies in thymoma is well established, only rarely in the literature have T-LBL and thymoma been seen in association and the relationship is poorly understood. Occasionally, distinction between the two can be difficult as immature lymphocytes in thymoma resemble T-LBL both morphologically and immunophenotypically. An accurate diagnosis is essential as treatments vary between these two entities.

Case Description: We present the interesting case of a 64-year-old male, former smoker, originally from Uzbekistan, with a mediastinal mass diagnosed as small cell carcinoma in his home country and treated with chemotherapy. After immigrating to the United States, a positron emission tomography (PET) scan demonstrated a large, metabolically active mediastinal mass. He presented to our institution where a biopsy with histomorphologic and immunohistochemical analysis was diagnostic of type B1 thymoma. He was lost to follow-up, but represented months later with B symptoms. Flow cytometry, cytogenetics, and bone marrow biopsy were diagnostic of T-LBL. Although he was started on chemotherapy, his disease progressed and he expired 6 months after initial presentation. Post-mortem analysis of the mediastinal mass revealed the co-occurrence of benign thymocytes and neoplastic T-LBL lymphoblasts, further confirmed as two distinct entities by T-cell receptor (TCR) sequencing.

Conclusions: Co-occurrence of thymoma and T-LBL is a well-documented, though poorly understood, phenomenon. Literature review for this phenomenon reveals that type B thymoma is most commonly associated with T-LBL in these co-occurrences. Most cases are diagnosed synchronously, though in metachronous cases, the diagnosis of thymoma has always preceded the diagnosis of T-LBL. Of note, recently developed LMO2 immunohistochemical stain is positive in malignant lymphoblasts but negative in benign thymocytes, allowing for post-mortem evaluation of this case to be determined as a synchronous presentation. These entities are difficult to distinguish and require a multimodal diagnostic approach including histology, immunohistochemistry, flow cytometry, cytogenetics, and TCR sequencing.

Keywords: Thymoma; T-lymphoblastic leukemia/lymphoma (T-LBL); T-lymphoblastic lymphoma; T-lymphoblastic leukemia; case report

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Introduction

Thymomas are a unique set of epithelial derived tumors that represent the most common neoplasm in the anterior mediastinum (1). Thymomas can vary drastically in histology, but generally have a lobulated architecture, and further classified based on the histologic appearance of the neoplastic epithelial cells; nuclei that have a spindle or oval shape and uniformly bland (Type-A thymoma) or whether they have a predominately round/polygonal appearance (Type-B thymoma) (2). The extent of infiltration of mature or immature non-neoplastic lymphocytes further subdivides type-B thymomas; B1-richest in lymphocytes, while B3-richest in epithelial cells. T-lymphoblastic leukemia/lymphoma (T-LBL) is a neoplasm of immature T-lymphoblasts that also presents frequently with mediastinal involvement (3). Distinguishing T-LBL from thymoma can be on occasion difficult, requiring a multimodality diagnostic approach incorporating histologic, immunohistochemical, flow cytometric and molecular data for an accurate diagnosis. Herein, we demonstrate diagnostic evidence for a rare phenomenon of a concurrent type-B1 thymoma and T-LBL and review the literature of this unusual phenomenon. We present this case in accordance with the CARE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-23/rc).

Highlight box

Key findings

- Co-occurrence of thymoma and T-lymphoblastic leukemia/lymphoma (T-LBL) can occur in any type of thymoma and may present synchronously or metachronously.
- Here we present a case of type B1 thymoma and T-LBL synchronous co-occurrence. Literature review suggests that in cases of co-occurrence, type B1 thymoma is the most common subtype observed and synchronous presentation is more common than metachronous presentation.

What is known and what is new?

- Co-occurrence of thymoma and T-LBL is well-documented, though rare and diagnostically challenging, phenomenon because benign thymocytes and malignant lymphoblasts share varies morphologic and immunophenotypic characteristics.
- We present an interesting case of co-occurrence that required histomorphologic, immunohistochemical, flow cytometric, cytogenetic, and genomic analysis to fully distinguish and confirm co-occurrence.

What is the implication, and what should change now?

- A multimodal diagnostic approach should be utilized when evaluating new diagnoses of thymoma, T-LBL in the mediastinum, or a suspected co-occurrence.

Case presentation

A 64-year-old male, former smoker, from Uzbekistan, was evaluated at our institution for dyspnea and right sided abdominal and chest pain. Significant medical history includes a previous large lung occupying mass diagnosed as small cell carcinoma in his home country for which he received chemotherapy with 2 cycles of etoposide/cisplatin and 2 cycles of docetaxel/cisplatin before he moved to the United States in late 2021 (per clinical note; histology and pathology report not reviewed). Imaging at an outside institution by positron emission tomography-computed tomography (PET-CT) demonstrated a 14.3 cm × 10.2 cm × 14.0 cm isolated mediastinal/lung mass occupying the right middle lobe extending into the lung hilum with increased uptake (standard uptake values of 4.5–10.6) (*Figure 1A*). No lymphadenopathy or other foci of disease were noted at this time. Core biopsy of the mass was performed at our institution and revealed bland epithelioid cells positive for cytokeratins (AE1/AE3, CAM5.1), PAX8, and p40, associated with copious immature lymphocytes positive for CD3 and TdT, diagnostic of a World Health Organization (WHO) type B1 thymoma (*Figure 1B-1F*). The patient was subsequently lost to follow-up.

Two months later the patient represented to our institution with persistent dyspnea and abdominal pain, but now with night sweats. Peripheral blood counts at this time revealed leukocytosis of 86.7×10^9–124×10^9cells/L with peripheral blasts (5–22%), hemoglobin of 11.6–13.4 g/dL and platelets of 30×10^9–57×10^9/L. Computed tomography (CT) of chest/abdomen/pelvis revealed the pre-existing mediastinal/lung mass with additional mediastinal, axillary, and intra-abdominal lymphadenopathy and hepatosplenomegaly. The patient underwent a bone marrow aspiration which revealed an excess population morphologically consistent with lymphoblasts (*Figure 2A*), and concurrent flow cytometry demonstrated a correlate population exhibiting an immunophenotype of CD45dim$^+$, CD1a$^+$, cytoplasmicCD3$^+$, CD4$^+$, CD5$^+$, CD7$^+$, CD8$^+$ and TdT$^+$, consistent with an aberrant cortical-stage T-lymphoblast population (*Figure 2B*). Cytogenetics revealed a complex karyotype (46,XY, add(1)(p13), del(5)(q15q33), t(6;8)(q21;q13), t(10;14)(q24;q11.2), del(12)(p11.2p13)[7]/46,XY[13]). Molecular studies regarding T-cell clonality were performed on both the

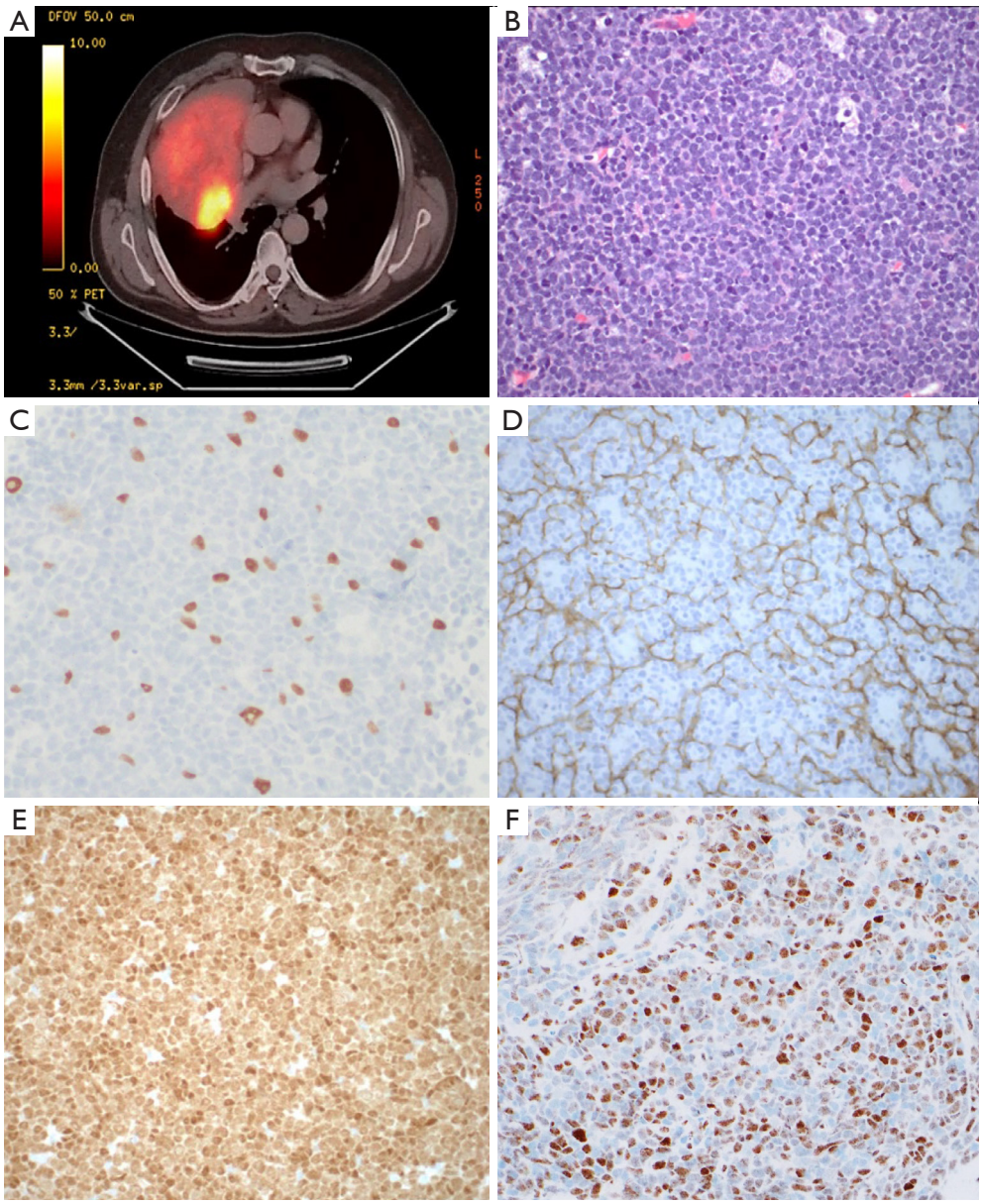

Figure 1 Thymoma. Radiologic and histologic imaging of mediastinal mass. (A) Positron emission tomography-computed tomography scan of chest reveals a large mediastinal mass. (B) Hematoxylin and eosin-stained core biopsy reveals diffuse lymphocyte population with occasional epithelial cells (×40). (C) p40 immunostain highlights malignant epithelial cells (×20). (D) Cytokeratin AE1/AE3 immunostain highlights malignant epithelial cells (×20). (E) TdT immunostain highlights lymphoblasts (×20). (F) LMO2 immunostain differentiates malignant lymphoblasts (positive) from benign thymocytes (negative) (×20).

mediastinal mass and bone marrow biopsy, which showed identical T-cell receptor (TCR) gamma chain monoclonal gene rearrangements (*Figure 2C*). We further evaluated both the bone marrow process and the mediastinal/lung mass by whole exome sequencing, with the following pathogenic mutations detected in both sites: NOTCH1 p.L1678P (33% mass, 36% bone marrow; exon 27), CDKN2A p.Y129X (78% mass, 93% bone marrow; exon 2) and PHF6 p.Q308X (95% mass, 93% bone marrow; exon 9). He was started on outpatient hyper-CVAD chemotherapy (cyclophosphamide, vincristine, doxorubicin and dexamethasone).

The clinical course was complicated by cerebral spinal

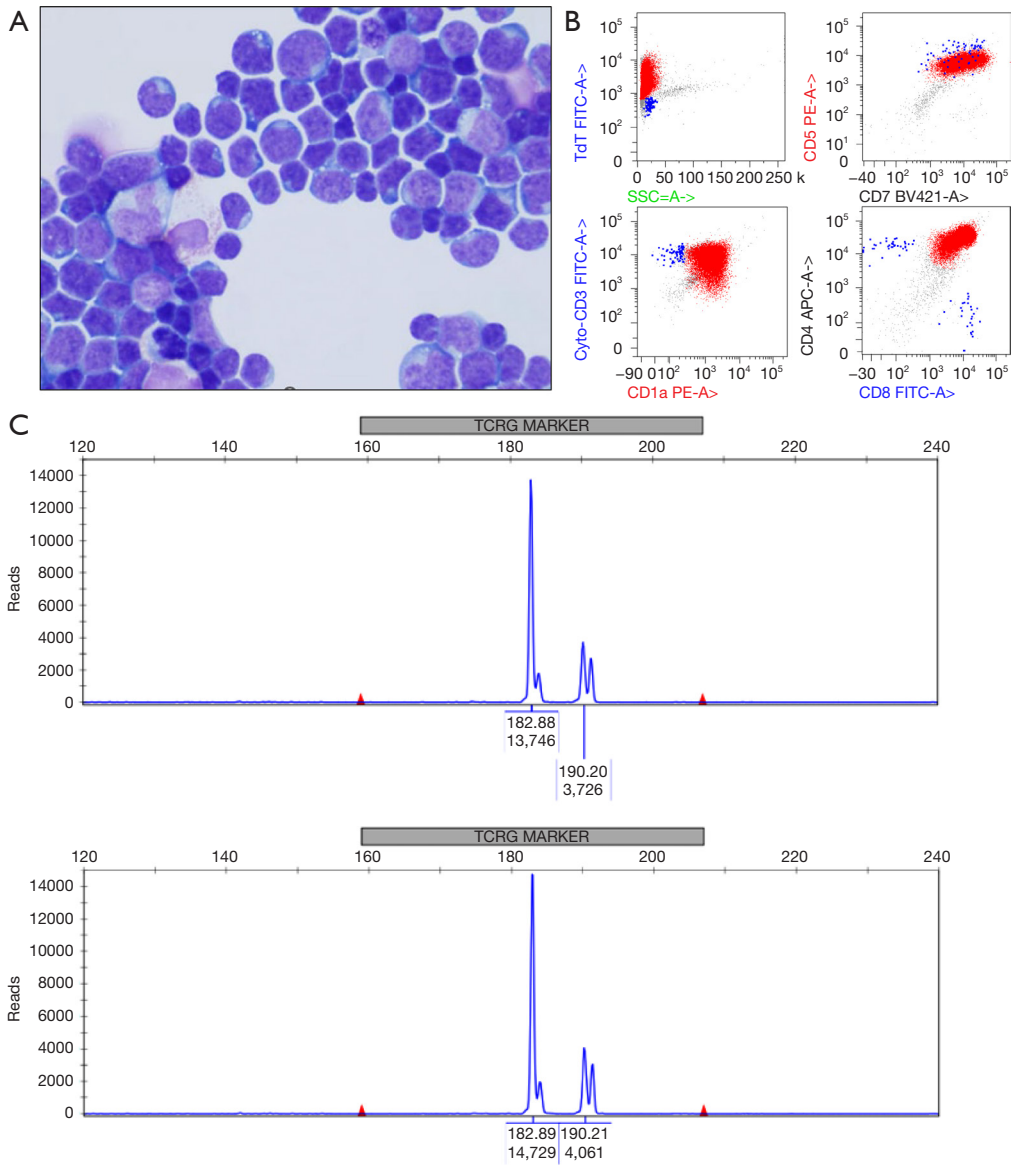

Figure 2 T-lymphoblastic lymphoma. Histologic, flow cytometric, and genomic data of bone marrow biopsy. (A) Hematoxylin and eosin-stained bone marrow aspirate reveals diffuse population of lymphoblasts (×100). (B) Flow cytometry demonstrates aberrant CD45dim$^+$, CD1a$^+$, cytoplasmicCD3$^+$, CD4$^+$, CD5$^+$, CD7$^+$, CD8$^+$ and TdT$^+$ cell population. (C) TCRG clonality sequencing demonstrates identical monoclonal populations in bone marrow biopsy (top) and mediastinal mass (bottom). TCRG, T-cell receptor gene.

fluid involvement by T-LBL, which required intrathecal methotrexate and cytarabine. In addition, shortly after starting chemotherapy the patient was found to be profoundly neutropenic with bacterial endocarditis, which required cessation of systemic chemotherapy after 1 cycle. After multiple hospital admissions due to persistent endocarditis as well as methicillin resistant *Staphylococcus aureus*-pneumonia and midbrain cerebrovascular accident, the patient transitioned to hospice care and died 6 months after initial presentation to our institution.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all

possible attempts were made.

Discussion

The incidence of thymoma and T-LBL, whether synchronous (herein defined as diagnosed within 6 months of each other) or metachronous (defined as diagnosed greater than 6 months apart), is a rare and poorly described process. In reviewing the literature, we identified 13 cases of T-LBL arising in association with thymoma, summarized in *Table 1* (4-13), with a median age of 61 (20–95 years) and a male predominance (10/13). Of those cases, most (9/13, 69%) occurred synchronously (diagnosed within 6 months of the first primary tumor), with metachronous cases showing a median interval from initial diagnosis to their second malignancy diagnosis of 8 years (6–30 years). Most patients (8/13, 62%) were diagnosed with a type-B thymoma, and of that subset most (5/8, 62%) were diagnosed with a type B1 thymoma. With the data available and based on when both diagnoses were established, most patients succumbed to their disease (7/13, 54%), with metachronous cases with notably poorer survival outcomes. Of note, we found no cases in the literature of a diagnosis of T-LBL preceding a diagnosis of thymoma.

While a molecular basis or conclusive evidence for a direct transformation from thymoma into T-LBL is lacking, other possibilities for a causative association exist. The risk for secondary malignancies in patients with thymoma has been described, though studies vary widely on the specific associated neoplasia. Some studies suggest non-Hodgkin lymphoma as one of the most frequent associated neoplasms (1,14,15), however other studies find solid tumors such as colorectal, lung, prostate and breast to much more common (16,17). Regardless, thymoma is known to alter immune function and leads to susceptibility to perturbations in T-cell immunity that can lead to paraneoplastic conditions such as pure red cell aplasia, myasthenia gravis, and hypogammaglobulinemia. Thus, it would seem plausible that altered immune function related to disturbed T-cell immunity caused by thymoma may lead to a predisposition to neoplasia, including T-LBL. Another possibility is that our patient, based on a presumed, though unconfirmed, diagnosis of thymoma possibly incompletely resected in his home country, received multiple cycles of adjuvant chemotherapy years prior, including alkylating and platinum-based agents that have been well described in association with secondary cancers. The genotoxic effect on hematopoietic progenitor cells from cytotoxic chemotherapy has been typically associated with clonal myeloid disorders such as a myelodysplastic syndrome or an acute myeloid leukemia, however acute lymphoblastic leukemias have also been described in this setting (18,19). In addition, there appears to be an increased incidence of thymoma among Asians and Pacific Islanders which may suggest an underlying genetic component.

Management for almost all thymomas is surgical resection with a well-defined role for radiation and chemotherapy depending on stage at presentation, while management for T-LBL includes multiagent chemotherapy with limited role for surgical intervention making diagnostic distinction from thymoma critical. A multimodality diagnostic approach is necessary including a combination of clinical presentation, morphology, immunohistochemistry, flow cytometry, molecular and cytogenetic findings that can each provide valuable information toward arriving at an accurate diagnosis. Our evidence for T-LBL is supported by an aberrant immunophenotype by flow cytometry, molecular studies including T-cell clonality and whole exome sequencing demonstrating essentially identical, characteristic T-LBL mutations (NOTCH1, CDKN2A) in both the mediastinal/lung mass and bone marrow and the immunohistochemical positivity for LMO2, which provides distinction between neoplastic and non-neoplastic T-precursor cells (20). The evidence for the type B1-tymoma includes histologic findings of bland scattered thymic epithelial cells positive for cytokeratins, PAX8, and p40 as well as the indolent clinical course prior to diagnosis of T-LBL. It should be noted that LMO2 immunostain was performed postmortem and confirms the synchronicity these two malignancies.

Conclusions

Our case and this literature review highlight a need for meticulous evaluation as rarely both the presence of neoplastic epithelial cells of a thymoma along with atypical T-lymphoblasts have potential to co-exist. While the co-occurrence of these two malignancies is rare, the prognosis is poor and careful analysis is required as treatment are different. Here we demonstrate the utility of LMO2 as an immunohistochemical marker of LMO2 as a specific marker for T-LBL lymphoblasts as well as provide a framework for a multimodal diagnostic approach to distinguish these two disease entities.

Table 1 Summary of reported cases of concurrent thymoma and T-LBL reported in the literature and the present case

Reference	Age (years)/sex	Presenting symptom(s)	Distribution of T-LBL*	Thymoma & T-LBL diagnostic interval	Thymoma type	T-LBL immunophenotype	Outcome
Macon *et al.* (4)	64/F	Acute pulmonary edema	Mediastinum, pleural fluid	30 years	B1	Positive for CD43, CD45, CD45RO, TdT; negative for CD75	Expired 24 days after 2nd presentation
Friedman *et al.* (5)	95/M	Back pain, cough, anorexia	Abdomen	Synch.	A	Positive for CD2, CD3, CD4, CD5, CD7, CD45, CD45RO; negative for CD8, CD10, CD19, CD20, CD22, CD43, CD68, kappa, lambda	Expired 10 days after presentation
Rovera *et al.* (6)	65/M	Dyspnea, fever, weakness, rash	Cutaneous, followed by hepatic and cerebral metastasis	3 months	AB	Positive for CD1a, CD3, TdT	Expired 8 months after 2nd presentation
Mizrahi *et al.* (7)	67/M	B symptoms	Mediastinum, diffuse lymph nodes, liver, kidney, skeleton	8 years	B1	Positive for CD1a, CD3, TdT	Expired 6 months after 2nd presentation
Boddu *et al.* (8)	50/F	Chest pain	Mediastinum	Synch.	B1	Positive for CD1a, CD3, CD5, CD10, CD99, TdT	Alive at least 2 years
Boddu *et al.* (8)	45/M	Weight loss, cough	Mediastinum, bone marrow	Synch.	A	Positive for CD3, CD7, CD33, CD34, CD45(dim), CD56, CD117, HLA-DR, TdT; negative for CD1, CD2, CD3, CD4, CD5, CD8, CD10	Not reported
Boddu *et al.* (8)	60/F	Chest discomfort	Mediastinum	Synch.	B1	Positive for CD2, CD3, CD4, CD5, CD7, CD8, TdT	Alive at least 8 months
Boddu *et al.* (8)	20/M	Referred	Mediastinum	Synch.	AB/B1/B2	Positive for CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD24, CD38, CD45(dim), CD52, TdT; negative for CD10, CD13, CD19, CD33, CD56, CD117, HLA-DR, MPO	Alive at least 1.5 years
Nishioka *et al.* (9)	43/M	Fatigue, blepharoptosis, then malaise dyspnea	Mediastinum, bone marrow	6 years	Type 1	Positive for CD2, CD3, CD5, CD7, CD8	Expired weeks after 2nd presentation
Ito *et al.* (10)	62/M	Fever, chest pain	Mediastinum	Synch.	AB	Positive for CD1a, CD3, CD4, CD5, CD7, CD8, CD99; negative for CD20	Alive at least 1 year
Le Clef *et al.* (11)	46/M	Pleural effusion, then diffuse lymphadenopathy	Diffuse lymphadenopathy	10 years	B2	Positive for CD2, CD3(dim), CD7, CD8(dim), TdT; negative for CD1a, CD4, CD5	Not reported
Ertel *et al.* (12)	62/M	None/incidental	Thorax	8 years	B1/B2	Positive for CD1a, CD3, CD99, TdT; negative for CD10, CD34	Expired 1 year after T-LBL diagnosis
Yılmaz *et al.* (13)	47/M	Fever, weakness, dyspnea	Mediastinum	Synch.	B2/B3	Not reported	Not reported
Present case	64/M	Chest and abdominal pain, then dyspnea, night sweats	Mediastinum, bone marrow, lymph nodes, liver, spleen	3 months	B1	Positive for CD1a, CD3, CD4, CD5, CD7, CD8, TdT	Expired 3 months after 2nd presentation

*, all cases include mediastinal mass positive for thymoma and as such when mediastinum is listed in this table; T-LBL is observed in the thymus/thymoma. M, male; F, female; T-LBL, T-lymphoblastic leukemia; Synch., synchronous (within 6 months).

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Footnote

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